

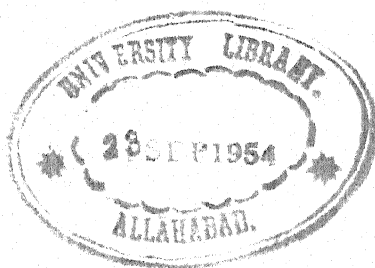
ORGANIC CHEMISTRY

The Chemistry of the Compounds of Carbon

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WASHINGTON & LEE UNIVERSITY

SECOND EDITION



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ORGANIC CHEMISTRY

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PREFACE TO THE SECOND EDITION

This is, in effect, a new textbook of organic chemistry. The earlier edition has been completely revised, modernized with respect both to theory and to industrial practice, and rewritten almost in its entirety. The aim remains the same—to guide the college student beginning the study toward an understanding of the fundamental principles of organic chemistry and some conception of its applications. The book is intended to serve as the basis for a year course and is designed particularly for those students whose formal training in the subject will probably end with such a course.

One compelling reason for a thorough revision lies in the almost incredible expansion of applied organic chemistry since 1936 when the first edition was published. This includes the rapid growth of fields such as plastics and synthetic detergents, which were already gaining importance at the earlier date, and the birth and large-scale development of many new ones. The latter is reflected in the terms, unknown even to the chemical profession in 1936, which are now used freely in the daily papers and often by the man in the street—"cat" crackers, GR-S rubber, nylon, DDT, sulfa drugs, penicillin, to mention only a few.

This constant and rapid expansion of everyday organic chemistry—to say nothing of the progress of research—imposes more and more insistently, year after year, the problem of what to include in an introductory year course and in the text upon which it is based. The solution cannot be found in the simple process of addition—down that road lies either a multivolume treatise or else a handbook of dictionary entries. The solution sought in this book is: to abandon any thought of being comprehensive; to reappraise the entire subject matter, old and new, and select carefully the illustrative material to be used; and, having decided to mention a principle or a product, to treat it in enough detail to give it meaning. The basis of selection and the order of presentation must be, necessarily, somewhat arbitrary. That is part of the price to be paid for a *text*—a book which will give the beginning student a reasonable chance to avoid that sense of utter confusion which Wöhler was experiencing in 1835 when he wrote, "Organic chemistry gives me the impression of a primeval, tropical forest . . . a monstrous and boundless thicket, with no way of escape, into which one may well dread to enter."

Our present advantage over Wöhler lies, of course, in the body of principles which have so largely converted an enormous and amorphous mass of facts into a coordinated body of scientific knowledge. The exposition of these principles, in terms comprehensible to the undergraduate, is fundamental. Happily, the "modern" principles—resonance, polarity, reaction mechanisms, etc.—have now been developed to the point where, within limits, they are capable of serving as useful tools in teaching and in comprehension. They are presented in this book as such tools—not as ends in themselves. As a teacher, I have sought to resist the author's temptation to tie up scientific principles in a series of neatly labeled packages for assembly in an early chapter. Instead, they are presented gradually, as the need develops, and as compounds are encountered which serve well for illustration. It is not that the newer concepts are inherently difficult but rather that to the beginning student almost *everything* is a new concept—those which chemists associate with Kekulé, Pasteur, and van't Hoff, equally with those connoted by names such as Gilbert Lewis, Ingold, and Pauling. In the initial stages, especially, it is necessary to protect the student against permanent confusion by avoiding the rapid introduction of too many new concepts, too many reactions, too much special nomenclature.

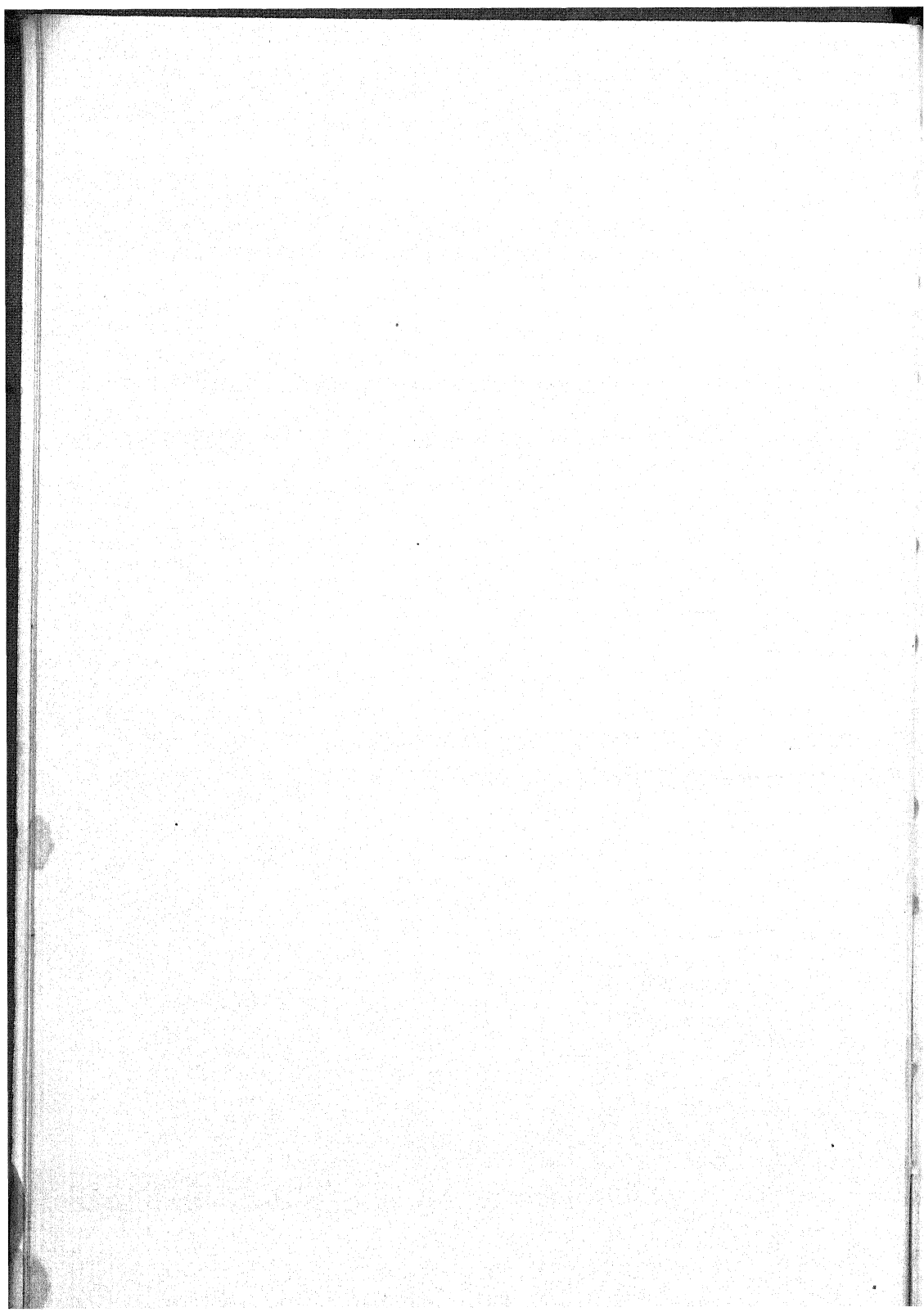
This revision has provided the opportunity to make some desirable changes both in the order of presentation and in emphasis. Aromatic hydrocarbons are introduced early, and aliphatic and aromatic monofunctional derivatives are treated in parallel, as in the first edition; petroleum and coal are now described in one chapter as joint sources of raw materials for the organic chemicals industry. Such an integrated treatment is, today, merely an acceptance of things as they are—a recognition of the facts of industry—today, when ethylene, benzene, and butadiene are being irrevocably scrambled on such a large scale in the synthetic rubber program, as are phenol with formaldehyde and phthalic anhydride with glycerol, and when petroleum has become the major source of toluene and the xylenes and a source of benzene and phthalic anhydride at least competitive with coal. But the more specialized aspects of aromatic chemistry—such as the mechanism of nuclear substitutions and the origins of directing and activating influences—are deferred to Chapter 22, with adequate cross references from earlier sections. Dyes and related topics (Chapter 25) are treated in some detail as a selected field which remains almost purely aromatic. In keeping with the progressive gain in their relative importance, an increasing proportion of total space in the book is assigned to aliphatic compounds. Fats, carbohydrates, and proteins, which formerly were described near the end, have been advanced and are now treated along with other poly-

functional aliphatic compounds. This rearrangement appears desirable pedagogically and has some special advantages for premedical students.

The author wishes to express sincere appreciation to his former colleagues, J. R. Taylor and W. C. Hunt, for valuable assistance in preparing and checking the manuscript; to Barbara McCaskill for typing it; to H. A. Lubs and W. R. Remington for their contribution in reading critically the sections on dyes and dyeing; and to H. E. Ritchey for his cooperation in proofreading. Permission to quote and to reproduce tabular material and one drawing are acknowledged in the appropriate places. Thanks are also due to the many companies and individuals who have generously supplied information requested for this book and to all those who made critical comments on the first edition. Further comments will be welcomed.

L. J. Desha

Lexington, Virginia
June, 1952



PREFACE TO THE FIRST EDITION

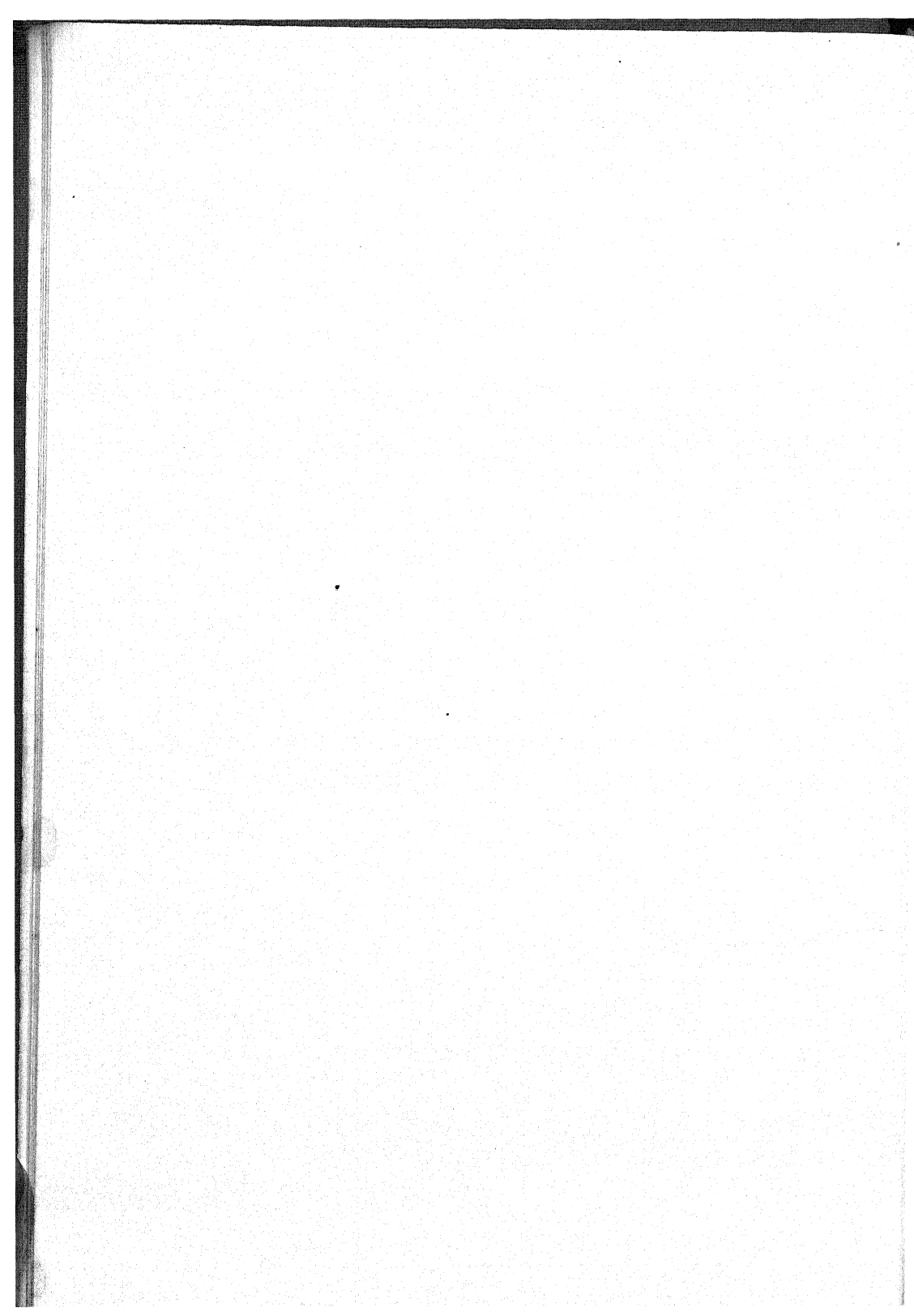
This textbook has been written for college students and primarily for those whose formal instruction in organic chemistry ends with a one-year course. It grew out of the realization that even the best students, completing my own course with the knowledge of many facts, had acquired but little appreciation of the underlying principles. Seeking a remedy, the approach and arrangement have been gradually changed. The guiding policy has been to consider compounds if, where, and as they serve usefully to illustrate and explain the general principles of organic chemistry. The resulting shift in emphasis is reflected in the chapter headings.

Broadly speaking, the subject matter is that ordinarily included in introductory textbooks; some things—which, perhaps, have come to be taken for granted—have been omitted; other topics, such as tautomerism, stereoisomerism, and the chemistry of the carbohydrates, have been amplified. The table of contents and the introductions to the five parts outline the general plan, which is integrated by many cross references. Attention is given to significant industrial relations and the value of work on identification is emphasized. The time requirement—and the thoroughness of instruction—will be influenced considerably by the number of review questions for which the student is held responsible.

I am indebted to more persons than can be named: To my students of the past ten years, whose responses to various experimental arrangements have guided and encouraged further efforts; to many industrialists—left in the anonymity which they prefer—for courteously supplying information; to James Lewis Howe, Larkin H. Farinholt, Catherine McDowell, J. R. Taylor, and R. D. Morrison for invaluable assistance in the preparation of the manuscript. I would also thank in advance all who may call attention to errors or to statements which should be revised.

L. J. Desha

Lexington, Virginia
August, 1936



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CHAPTER 1

THE CHEMISTRY OF MOLECULES

Organic chemistry is the chemistry of the compounds of *carbon*. Logically, it is a chapter of general chemistry, along with those which treat of the compounds of sulfur, the compounds of nitrogen, etc. But carbon compounds are too numerous to be studied effectively in this way. Something like 500,000 are known—probably more than ten times as many as all noncarbon compounds together. Practically, therefore, the “carbon chapter” of general chemistry swells into an independent book and separate courses are set up for the study of *Organic Chemistry*.

1.1 The name *organic* arose from the fact that the first carbon compounds studied (aside from the oxides of carbon and the inorganic carbonates) were all obtained from the bodies of plants or animals—that is to say, from *organized* or living things. The term still serves usefully to suggest some very important relations. For the most part, all plant and animal bodies are composed of carbon compounds, and all the processes by which these are formed and transformed during the growth and decay of living things are reactions of organic chemistry. Hence, this science is fundamental to any intelligent study of the principles of agriculture, animal husbandry, biology, nutrition, and medicine. Furthermore, as will appear, plant and animal debris of former ages has been converted in the course of geologic time into coal, natural gas, and petroleum. These substances, with the wood, cotton, grain, fats, and other present-day products of plant and animal life, furnish nearly all the raw materials for great industries which produce hundreds of organic compounds not found in nature. Such products of synthetic organic chemistry include dyes, drugs, explosives, rayon, plastics, and an almost endless variety of other substances contributing to the power, convenience, and pleasure of modern life.

1.2 The properties as well as the number of carbon compounds make it convenient to set aside organic chemistry as a separate course of study. Because of their physical properties, special laboratory techniques are often required for separating and purifying them. All organic compounds are combustible, and many are readily inflammable—thus calling for suitable precautions against fire in working with them. But, aside from combustion—and the rapid decompositions of a few explosives—most of the reactions of organic compounds are curiously slow. Conse-

quently, many laboratory and factory operations require condensing systems, pressure vessels, or other special equipment by means of which substances may be heated together at relatively high temperatures for long periods of time; many others require the presence of selected catalysts in order to get results with reasonable speed.

The general slowness of organic reactions contrasts sharply with the speed of many inorganic chemical changes. Most of the latter that the student has encountered in general and in analytical chemistry—which are, for the most part, reactions in solution—go to completion within the time required for mixing the reactants. This difference in speed of reaction arises from the fact that, broadly speaking, inorganic chemistry is the chemistry of *ions* while organic chemistry is the chemistry of *molecules*. In order to clarify this statement, it is necessary to review¹ and emphasize the fundamental distinction between electrovalent and covalent linkages.

1.3 Electrovalence. Most noncarbon compounds can be described as ionic or electrovalent because they exist as aggregates of *ions*—electrically charged particles. Ions are formed by the *transfer* of one or

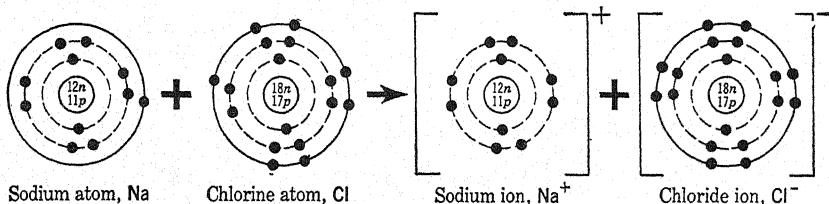
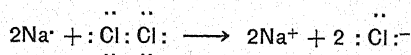


FIG. 1-1 Formation of an ionic compound. The elements sodium and chlorine react by *electron transfer* to form the typical electrovalent, ionic compound sodium chloride. By losing the lone electron of its valence shell, the sodium atom becomes a sodium ion, which carries a unit positive charge because the remaining 10 electrons do not balance the 11 protons of its nucleus. When a chlorine atom gains an electron, it becomes a chloride ion with a unit negative charge (18 electrons, 17 protons). Note also that the sodium ion has stripped down to an outer (second or L) shell of 8 as in the inert gas neon and that the chlorine ion has a completed (third or M) shell as in argon.

more electrons from the outer, or valence, shell of one atom to that of another. This is illustrated in the formation of sodium chloride from its elements, as indicated in Figure 1-1 and by the following equation²:



¹ For more details than can be given here, refer to any standard modern text for first-year college chemistry.

² In this equation the symbols Na and Cl are used to represent the so-called *kernels* of the sodium and chlorine atoms—that is, the nucleus and all electrons *beneath* those of the valence shell. The latter are indicated by dots.

Each chloride ion carries a *unit* negative charge equal to that of the electron gained, that is, 4.805×10^{-10} esu (electrostatic unit), and each sodium ion carries a positive charge of this identical magnitude. Ions formed by the gain or loss of two or more electrons carry corresponding numbers of such unit charges.

The crystals of electrovalent compounds consist of clusters of positive and negative ions held together in a regular pattern by the mutual attractions of their opposite charges. The pattern of the *crystal lattice* for sodium chloride, as revealed by the method of X-ray spectroscopy, is shown by the model pictured in Figure 1-2. Such a model makes it clear that no one sodium ion is paired off with any chloride ion. In other words, there is no such thing as a *molecule* of sodium chloride or other electrovalent compound—unless we choose to think of each entire crystal as a giant molecule. A formula such as NaCl or Na^+Cl^- is merely a convenient statement of the *relative* numbers of the two kinds of ions.

The electrical attraction of an ion in a crystal extends *uniformly in all directions*. As many negative ions as space permits¹ will group around any positive ion; this layer of negative ions in turn attracts a layer of positive ions; and so, as this process continues, the entire crystal is bound into a rigid unit. The strength of such electrostatic attractions is indicated by the physical properties of ionic crystals. These are usually hard and rigid, not easily deformed by pressure. They have high melting points, *e.g.*, 801°C for Na^+Cl^- . This means that much heat must be added to give the ions enough kinetic energy to overcome attractions, break away, and disrupt the crystal arrangement. When the temperature drops a little below the melting point, ionic attractions again prevail and recrystallization sets in, restoring the former orderly arrangement.

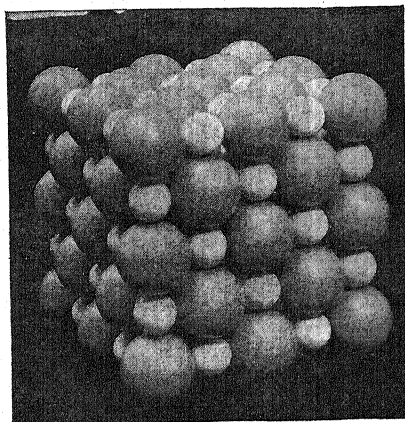


FIG. 1-2 Model showing the arrangement of sodium ions (small spheres) and chloride ions (larger spheres) in the crystal lattice of sodium chloride. Each ion in the interior of the crystal is surrounded symmetrically by six ions of the opposite charge.

¹ In the crystals of sodium chloride, six Cl^- ions are able to pack around each Na^+ ion and each Cl^- ion shares its attraction equally among six Na^+ ions. In cesium chloride, Cs^+Cl^- , the corresponding number is eight because the Cs^+ ion is much larger than Na^+ .

When crystals of sodium chloride are placed in water, ions in the surface layer are attracted by water molecules and pass into solution; and, as fresh layers are thus exposed, this process continues and the crystals fall apart or dissolve. Because the solute particles are charged, water solutions of ionic compounds are good conductors of electricity. In fact this ability to conduct the electric current in solution and when fused¹ is the quickest and most general practical method for differentiating between electrovalent and covalent compounds (Sec. 1.5).

It is also largely because the solute exists as charged ions that reactions between electrovalent compounds in solution are nearly always rapid. The ions present in each solution are already, by reason of their charges, in what may be called an activated condition—ready to react. Ordinarily, it suffices simply to mix them and thus provide opportunity for contacts.

1.4 The elements that form electrovalent compounds are usually those which like sodium and calcium have 1 or 2 electrons in the valence shell and, by losing them, can strip down to an under shell of 2 or 8, or those which like chlorine and oxygen have 7 or 6 electrons in the valence shell and by gaining 1 or 2 can complete a shell of 8. This illustrates a general tendency of the elements to attain—in one way or another—an outer shell like one of the inert gases. Hydrogen is satisfied with 2, as in helium, and lithium readily loses its lone valence electron to strip down to the under shell of 2 in the lithium ion, Li^+ . Most of the other elements tend toward an outer shell of 8 (an *octet*) as in neon and argon. Eight is usually the maximum, but some of the heavier elements are able to accommodate expanded valence shells containing a larger number.

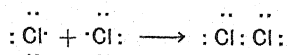
1.5 Covalence. Another way in which an atom can acquire the valence shell of an inert gas is through the process of *electron sharing*, which results in the formation of covalent linkages or bonds. In the simplest possible instance, two hydrogen atoms pool their lone electrons in forming the hydrogen molecule:



By sharing this pair each hydrogen atom acquires the helium shell of two and a stable molecule is formed. The nucleus of (ordinary) hydrogen is a single proton with unit positive charge, and two of them repel each other. They are held together in the molecule through attraction for and by the shared pair of electrons. Chlorine atoms unite in similar

¹ Crystals of electrovalent compounds do not conduct because the ions are not able to move; fusion (melting) destroys the rigid structure of the crystals and permits free movement.

fashion to form the chlorine molecule,



in which each atom has an outer shell of eight as in neon and argon. In sharp contrast with electron transfers, which result in the formation of charged ions, the processes of electron sharing illustrated in the above reactions do not confer a charge upon either atom but result in the formation of electrically neutral *molecules*.

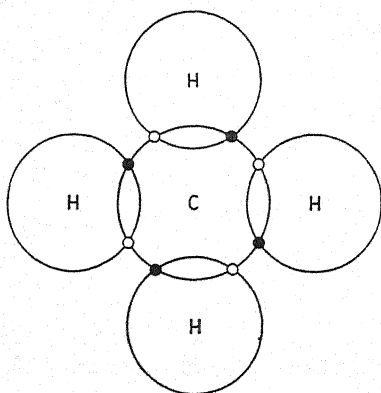


FIG.1-3

FIG. 1-3 Diagram of the methane molecule, CH_4 . Through the formation of four covalent linkages with hydrogen, the carbon atom has built up its valence shell to an octet, as in neon, and each hydrogen atom has acquired the stable electron pair of helium. Blackened circles have been used to represent the electrons assumed to have come originally from the carbon atom and open circles for those from the hydrogen atoms.

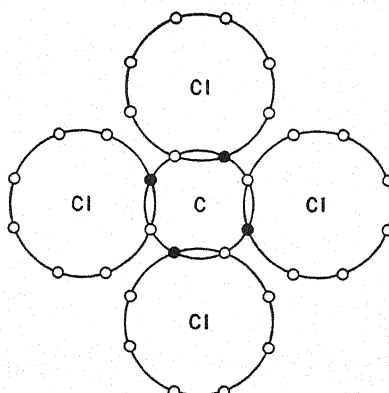
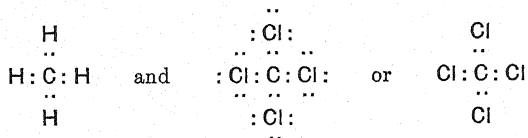


FIG.1-4

FIG. 1-4 Distribution of the valence electrons in a molecule of carbon tetrachloride, CCl_4 . Through electron sharing, each of the five atoms in the molecule has acquired a completed octet.

Electron sharing is of fundamental importance in organic chemistry because it is the process by which *carbon* regularly enters into chemical combination. The atom of carbon (atomic number 6) has four valence electrons and in substantially all carbon compounds has completed its octet by forming four covalent bonds. This is illustrated in the formula for methane, CH_4 , which is diagramed in Figure 1-3. The important fact that carbon likewise forms covalent linkages with strongly electronegative elements (Sec. 1-9) such as chlorine is illustrated in Figure 1-4, representing carbon tetrachloride, CCl_4 .

1-6 Drawings like those in Figures 1-3 and 1-4 are too cumbersome to be useful except in an introductory explanation. For greater convenience, they are condensed into formulas (Sec. 1-13) such as



The two dots placed between symbols represent the shared pair of electrons which constitute a covalent bond. This useful convention must not be misunderstood to imply that electrons are ever stationary. We know that they are always in rapid motion between and about the nuclei they join. There is strong evidence, however, that at a given instant the bonding electrons are most likely to be found *between* the nuclei and in or near the line joining their centers. We may therefore think of the dots as indicating roughly the *most probable* positions of the electrons.

It must be understood, further, that once a covalent bond is formed there is no difference between the electrons of a pair (except as explained in Sec. 1-7). The carbon atom in a C:H bond has as much claim on the electron which came from hydrogen as on the one which it contributed, and vice versa. The use of different shadings for the electron symbols in Figures 1-3 and 1-4 is merely a "bookkeeping" device to account for the valence electrons of the several atoms.

1-7 On a somewhat more advanced level of study, two further points with regard to covalent bonds should be mentioned. The electrons forming a covalent bond *do not travel together*; rather, they tend to stay as far apart from each other as possible because of the repulsion of their like charges. The *pairing* which relates them is described by physicists somewhat as follows. Electrons have a property described as "spin," which means that they behave like tiny bar magnets. Two electrons are paired when they are so oriented that the lines drawn from their north to their south poles point in exactly opposite directions. Another condition for pairing is that both electrons must be in the same quantum level.

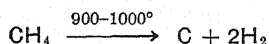
With very few exceptions, molecules contain an *even* number of electrons, all of which are paired. Often, however, some of these pairs are not *shared*, *e.g.*, each of the chlorine atoms in carbon tetrachloride (Fig. 1-4) carries three unshared pairs.

1-8 **Molecules** are discrete particles of matter in which some definite numbers of atoms, of the same or different kinds, are held together by covalent linkages, *e.g.*, H_2 , Cl_2 , H_2O , CH_4 , CCl_4 . In general, these particles persist unaltered in the solid, liquid, and gaseous states and in solution. Any molecule must contain the same number of (nuclear) protons and (extranuclear) electrons and therefore is electrically neutral.

For this reason substances composed of molecules are generally non-conductors in the liquid state and, with some exceptions, when in solution. As a class these compounds are much less soluble in water than are ionic compounds; conversely, they are usually much more soluble in organic liquids such as carbon tetrachloride.

The crystals of covalent compounds have a definite lattice pattern in most of which *the units are molecules*. These crystals differ quite sharply in physical properties from those of typical ionic compounds. The crystals of CCl_4 are soft, easily deformed by pressure, and melt at the low temperature of -23°C ; the hard, rigid crystals of Na^+Cl^- melt only at 801°C . Such differences—which are quite typical—indicate that the attractions *between* molecules are rather weak, because so little energy is needed to overcome them and destroy the crystal lattice. Boiling points (which are a measure of the attractions between the particles of liquids) tell a similar story. Ionic Na^+Cl^- must be heated to 1413°C to cause boiling, while 76.8°C suffices for covalent CCl_4 . The attractions between CH_4 molecules are so very slight that this gas must be cooled to -161.5°C in order to liquefy it at atmospheric pressure.

But *within* a molecule, the forces represented by covalent linkages are often very strong. Thus, in sharp contrast to the -161.5°C at which the attractions between methane molecules are overcome and the liquid boils, temperatures approaching 1000°C are required to break the bonds between its atoms and convert it into elementary carbon and hydrogen:



Since at least one covalent bond must be broken in almost any reaction of an organic molecule, we begin to see some reason for the general slowness of organic reactions and the practical need for speeding them up by high temperatures or by catalysts.

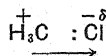
1.9 Charges within Molecules. It is important to grasp firmly the difference just emphasized between the *permanently charged ions of electrovalent compounds* and the *electrically neutral molecules of covalent compounds*. It must not be concluded, however, that electrical differences are nonexistent in molecules or unimportant in their behavior. For, although every molecule is electrically neutral, one region within it may be relatively negative and another correspondingly positive. This situation may arise in various ways, of which the simplest and one of the commonest is the following.

When two atoms of the *same* element are joined by a covalent bond, as in the molecules $\text{H}:\text{H}$ and $\text{Cl}:\text{Cl}$, we are forced to conclude that the shared electrons are attracted equally by both nuclei and that their

most probable position¹ is midway between. But this is rarely true when the bonded atoms are different, for the nuclei of different atoms vary considerably in their *electronegativity*, or attraction for electrons. These differences have been estimated (largely from the heats of formation of substances) and are recorded in what is known as Pauling's electronegativity scale,² from which the following values are taken:

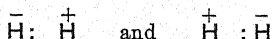
Na	Mg	Al	H	I	C	S	Br	Cl	N	O	F
0.9	1.2	1.5	2.1	2.4	2.5	2.5	2.8	3.0	3.0	3.5	4.0

Since chlorine is more electron-attracting than hydrogen, iodine, and carbon, it is logical to assume that in each of the following molecules the most probable position of the bonding pair is displaced somewhat in the direction of the arrows:



This means that the chlorine atom in each of these molecules carries a *fractional* negative charge and the atom to which it is joined is correspondingly positive. It means also that the linkages shown are not strictly covalent (as in H:H) but are *partially ionic*³ in character. The displacement is described as an *inductive* effect of the chlorine atom. Such fractional charges as we are considering here are conveniently indicated by the symbols $+\delta$ and $-\delta$ to distinguish them from the *unit* plus and minus charges which arise through electron transfer and ionization.

¹ This does not exclude the chance that occasionally, for a brief instant, both electrons will be quite close to one or the other nucleus. At such times, the molecule may be regarded as momentarily, but *only* momentarily, polarized (Sec. 3-8) as suggested by formulas such as



² Some clue to the origin of "electronegativity" is given by the following observations. With atoms in which the positive nuclear charge is shielded by the same number of electron shells, electronegativity increases with the nuclear charge, *e.g.*,

C (+6)	N (+7)	O (+8)	F (+9)
2.5	3.0	3.5	4.0

Electronegativity decreases with the increasing numbers of electron shells which shield the positive nucleus, *e.g.*,

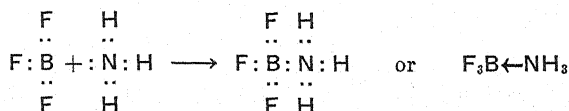
F (2)	Cl (3)	Br (4)	I (5)
4.0	3.0	2.8	2.4

³ For example, certain measurements make it possible to calculate that the covalent linkage in gaseous H:Cl is approximately 17 per cent ionic. In other words, the displacement of the bonding pair by the inductive attraction of the chlorine atom is 17 per cent of what would be required for ionization into H⁺ and Cl⁻.

Another way to indicate an inductive effect is illustrated as follows:



Charges within molecules sometimes originate also in the way illustrated by the union of the two compounds boron trifluoride and ammonia:



The boron atom, belonging to the third column of the periodic system, has only three valence electrons, and in BF_3 it has a share in only six. It completes an octet by accepting the unshared pair on the nitrogen atom of ammonia. The addition compound is polar, with a $-\delta$ charge on boron and a $+\delta$ charge on nitrogen. Bonds like this, to which one atom contributes *both* electrons of a shared pair, are called *coordinate covalences*.¹ They are usually indicated by an arrow between two symbols, pointing away from that of the donor atom.

Molecules such as those of the two types just described are said to be permanently *polarized* and are called *dipoles*. Later, we shall show in some detail how the resulting fractional charges may influence the chemical behavior of compounds. For the present it suffices to make the general observation that the $-\delta$ end of a dipole is a likely point of attack by a reagent which is electron seeking and, conversely, that a reagent which has electrons to contribute is likely to attack the $+\delta$ end of a polarized molecule.

1.10 Dipole Moments. The existence of fractional charges within molecules is shown most conclusively by the physical property known as dipole moment. When dipolar compounds in the gaseous state or in solution are placed between electrically charged plates, the molecules tend to turn themselves so that their positive ends are directed toward the negative plate, and vice versa. The result is a change in the electrical capacity of the system, from the measurement of which it is possible to calculate the *dipole moment*. This property is useful in comparing the relative polarities of different compounds. For example, methane has zero moment (no polarity), while the value for the gaseous molecule of methyl chloride, $\text{H}_3\text{C}:\text{Cl}$, equals 1.87×10^{-18} esu or 1.87 Debye units.²

¹ A preferable term, *dative covalence*, which is much used by English scientists, has not been generally accepted in this country.

² The dipole moment of a molecule is defined as the distance in centimeters between the centers of opposite charge times the magnitude of the charge. Suppose, for example, there exist unit plus and minus charges (4.805×10^{-10} esu) on two points 1

1.11 Molecular Architecture. Another important property of covalent bonds is that they are *directional*. Hence, when atoms are joined by electron sharing, their relative positions are fixed¹ and each covalent molecule has a definite architectural pattern. A simple example is the water molecule in which, we now know, the arrangement is such that lines joining the hydrogen atoms to the oxygen make an angle of approximately 111° , as shown in Figure 1-5. The observed dipole moment of

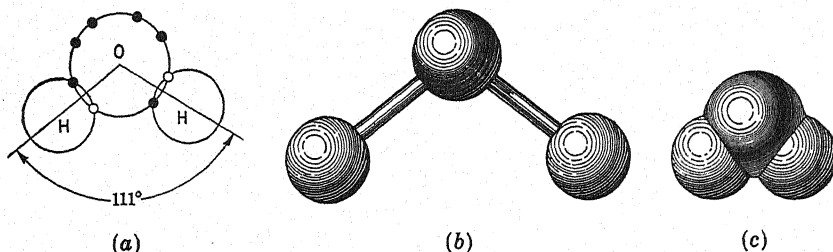
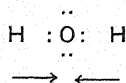


FIG. 1-5 The water molecule. Relative positions of the oxygen and the two hydrogen atoms are shown by the drawing (a) and by two kinds of mechanical models (b) and (c).

water is consistent with this arrangement of its atoms. If they lay in a line



the electronic displacements indicated by the arrows would cancel and give zero moment. Actually, water is a polar substance with a relatively high $-\delta$ charge on the oxygen atom. A suitable calculation shows that the bond angle of 111° should give approximately the observed dipole moment of 1.84 D. The ability of water to dissolve so many electrovalent compounds is intimately associated with its own polarity.

The concept of a definite *molecular structure* is fundamental in the study of the compounds of carbon. The molecule of methane is *not* flat, with the carbon and hydrogen atoms lying in a plane, as Figure 1-3 implies. Instead, the four hydrogen atoms are so situated that lines drawn from

angstrom apart. (The angstrom, \AA , is equal to 1×10^{-8} cm.) The resulting dipole moment would be 4.805×10^{-10} esu $\times 1 \times 10^{-8} = 4.805 \times 10^{-18}$ esu, or 4.805 D. (The Debye unit, D, is defined as equal to 1×10^{-18} esu.)

¹ We may neglect here the limited vibrational and rotational motions which actually occur but do not affect materially the relative positions of the atoms.

them to the carbon atom make equal angles in space, as suggested by the model shown in Figure 1-6. The calculated value for this angle is $109^{\circ}28'$, and values close to it have been measured in many organic compounds, such as CCl_4 and $\text{C}(\text{CH}_3)_4$, in which four like atoms or groups are attached to a carbon atom.

1.12 Molecular models are often helpful in grasping this fundamental idea of the definite structures of organic molecules and thinking in terms of it. The commonest type of mechanical model consists of balls of various colors which can be joined by suitable pins. Holes in the balls are so bored that the inserted pins make angles equal (roughly) to those measured for the atoms represented, and the number of holes is made equal to the usual valence of the element. Figures 1-6 and 1-7 represent such models for methane and ethane, C_2H_6 . In another type of model (Figs. 1-8 and 1-5c) the balls are scaled according to the measured effective diameters of different atoms. They are also cut away so that their

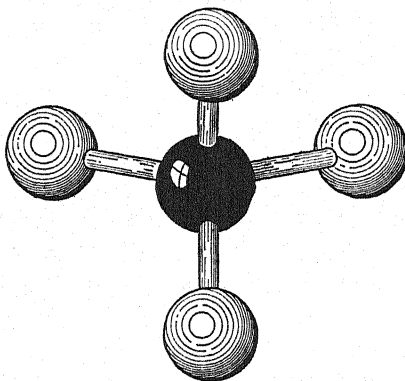


FIG. 1-6 Mechanical model of the methane molecule showing three-dimensional structure.

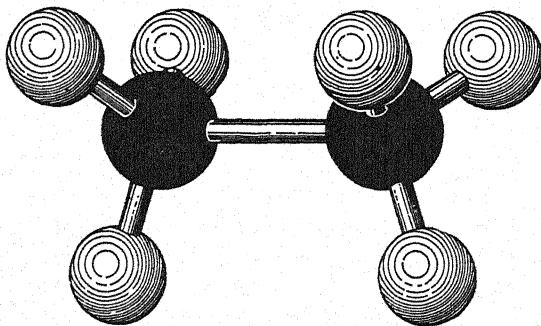


FIG. 1-7 Model of the ethane molecule, C_2H_6 .

centers come closer together. This corresponds with an actual shortening of the distances between centers when atoms are joined by covalent bonds. (When two atoms are covalently bonded, there is a certain mutual penetration of their electron atmospheres.)

All such mechanical models have obvious limitations—notably the necessity for using some kind of wooden or metal pin to represent a

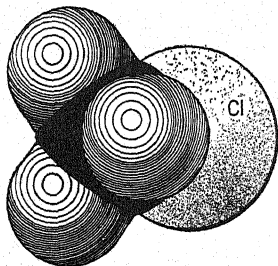
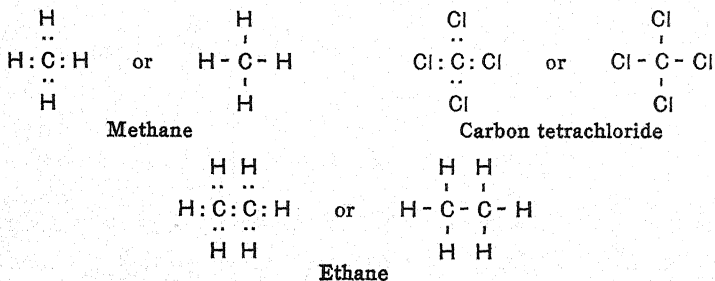


FIG. 1-8 Scale model of the molecule of methyl chloride, CH_3Cl , showing the relatively large effective diameter of the chlorine atom.

linkage formed by sharing a pair of fast-moving electrons. But, with a reasonable amount of imagination, models can be enormously helpful and, for certain purposes, are almost indispensable. The student is urged to use them at every opportunity in order to develop as quickly as possible the habit of thinking of organic molecules in terms of their three-dimensional or *space* structures.

1-13 Structural Formulas. Certain consequences of space relations (Chaps. 4 and 17) require the use of mechanical models or of drawings which represent them. Ordinarily, however, organic molecules are symbolized by conventional *structural formulas* of the types:



A covalent bond between two atoms may be represented either by a pair of dots or by a single short line. Both symbols are understood to have exactly the same meaning. The line is more convenient and is generally used; but, when it is desirable to call special attention to the shared electrons which constitute the bond, the dots are more suggestive.

In learning to use structural formulas it is important to write down separately the symbol of every atom in the molecule, repeating it as often as that atom occurs. It is important, also, to make sure that the number of bonds connecting each atom with its neighbors is equal to the valence of that atom. Among covalent compounds we may say that *the valence of an atom is the number of pairs of electrons which it shares with other atoms*.¹ The student should assume for the present that the following valences are constant in organic molecules:

Carbon.....	4	Hydrogen.....	1
Oxygen.....	2	Halogens (F, Cl, Br, I).....	1

¹ This definition has to be modified somewhat for coordinate covalences.

Some exceptions, and the *variable* valences of nitrogen and sulfur, will be considered later.

Using valence rules alone, it is possible to write correct structural formulas for a few simple organic molecules. For all the more complicated molecules these rules have to be supplemented by much additional information (though, even here, they are important in eliminating *impossible* structures, such as one containing a carbon atom with *five* valences). The nature and sources of the further information needed for determining the structures of organic molecules will be considered as the study proceeds. In the meanwhile, the student must assume that the structural formulas presented are based upon sound evidence. He will be expected to use them regularly, in writing equations and elsewhere, because facility in doing so is a prerequisite to mastering organic chemistry.

1-14 Molecular Formulas. A formula such as C_2H_6 or $C_6H_{12}O$, which simply states *how many* atoms of each kind are present in the molecule of a substance, is called a *molecular* formula. Courses in general chemistry describe how these are determined for simple compounds like water and carbon dioxide with the aid of two essential operations: (1) an *accurate* determination, by synthesis or analysis, of the percentage of each element contained in the compound; and (2) a determination of the molecular weight, by vapor density or otherwise. Molecular formulas of organic compounds are obtained by applying these same principles, whether it be to a simple compound like CH_4 or to complex molecules such as $C_{12}H_{22}O_{11}$ (cane sugar) or $C_{20}H_{24}N_2O_2$ (quinine).

A molecular formula, as such, tells us absolutely nothing about the arrangement of the atoms within the molecule, but the information which it conveys is necessary before beginning to establish a correct structural formula.

1-15 The following is a simple example of how the molecular formula of an organic compound is obtained. Assume that a certain substance is found by an accurate analysis to contain 80 per cent of carbon and 20 per cent of hydrogen. Then

$$\text{Weight of C : weight of H :: 80 : 20}$$

Dividing these numbers by the *gram-atomic weights* of carbon and hydrogen, respectively, we have

$$\text{Gram atoms of C : gram atoms of H :: } \frac{80}{12} : \frac{20}{1}$$

$$\text{Gram atoms of C : gram atoms of H :: 6.67 : 20}$$

$$\text{Gram atoms of C : gram atoms of H :: 1 : 3}$$

That is, for 1 gram atom of carbon there are 3 gram atoms of hydrogen, and for 1 *atom* of carbon there are 3 *atoms* of hydrogen. This is expressed by the formula CH_3 , which is known as an *empirical* formula. Now assume, further, that one determines

the vapor density of the substance (which happens to be a gas) and from this is able to calculate a molecular weight of approximately 30. The molecular weight corresponding to CH_3 is only 15; hence the molecular formula must be $(\text{CH}_3)_2$ or C_2H_6 . Actually, the data given are correct for the compound ethane.

In summary: The empirical formula, derived from a correct analysis, gives accurately the *relative* numbers of each kind of atom in the molecule. The molecular weight tells whether this empirical formula must be multiplied by 1, 2, or some other *whole number* to give the molecular formula.

Questions

1. Following the rules and conventions explained in Section 1-13, write structural formulas for the following covalent molecules, indicating each valence bond by a single short line or dash: (a) CH_2Cl_2 ; (b) CHBr_3 ; (c) C_2H_6 ; (d) $\text{C}_2\text{H}_5\text{Br}$; (e) C_3H_8 ; (f) CH_4S (assuming that the valence of sulfur is 2 as in H_2S); (g) CH_5N (if the valence of nitrogen is 3 as in ammonia).

2. Rewrite the structural formulas of the above compounds using a pair of dots to indicate the shared electrons which form each valence bond.

3. Rewrite these formulas again, using for each valence bond an arrow pointing in the direction in which the bonding pairs of electrons should be displaced (according to the electronegativity scale in Section 1-9). Which of these molecules would, in your judgment, have zero dipole moments? Which would clearly be polarized molecules? Why would you need further information about some of them?

4. (a) Show that for a molecule of the formula $\text{C}_2\text{H}_6\text{O}$ it is possible to write two different structural formulas each of which satisfies the usual valence rules. (b) Do the same for a molecule having the formula $\text{C}_3\text{H}_7\text{Br}$. (c) Can you construct a *third* structural formula for either of these molecules if you adhere to the valence rules?

5. It has been emphasized in Section 1-11 that covalent bonds are directional. What evidence can you offer that electrovalence is *not* directional?

6. Analysis of a certain liquid showed that it contains 82.7 per cent carbon and 17.3 per cent hydrogen. A 0.235-gram specimen of the liquid when vaporized occupied a volume of 90 cm^3 (reduced to standard conditions). (a) What is the empirical formula of the substance? (b) What is its molecular formula? (c) Write as many structural formulas as are possible.

CHAPTER 2

CARBON CHAINS; HOMOLOGY; ISOMERISM

Compounds that contain carbon and hydrogen *only* are called hydrocarbons. This simplicity in elementary composition makes them a suitable group with which to begin the study of organic chemistry. Furthermore, as will appear later, the chemistry of carbon compounds containing other elements, such as oxygen, the halogens, sulfur, and nitrogen, is greatly clarified by relating them to the hydrocarbons.

2.1 Hydrocarbons are of first-rank industrial importance as well as of scientific interest. The enormous quantities of natural gas and petroleum annually produced and their commercial products—including gasoline, fuel oil, lubricants, etc.—consist almost entirely of mixtures of hydrocarbons. In an age of oil-burning ships, locomotives, and diesel trucks, gasoline-propelled motor cars and aircraft, and an industrial system founded on oil-lubricated machinery, the role of these hydrocarbons is obvious enough. The gas and tar recovered when coal is coked yield large amounts of other hydrocarbons, such as benzene and naphthalene. These are the raw materials for major industries which, through various chemical transformations, convert them into dyes, drugs, explosives, plastics, and many other products now regarded as indispensable to civilized man.

Several hundred different hydrocarbons are known but their study does not present the difficulty this number suggests. Simplification results from the fact that they can be grouped into a few families, within each of which there are marked resemblances between individuals. Hence, a knowledge of the properties and relations of a few typical members of each family furnishes most of the essential information about the many others.

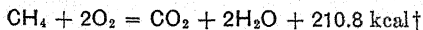
This chapter deals with one of the families of open-chain or *aliphatic* hydrocarbons, of which methane and ethane are simple and typical members.

2.2 Methane, CH_4 , is a colorless, odorless gas which liquefies at -161.5°C and freezes at -182.5°C . Water dissolves traces only, but it is much more soluble in organic liquids such as acetone and ether. Methane composes about 85 per cent of the average natural gas and is an important component of most other industrial fuel gases such as those

from coke ovens and petroleum-cracking stills. It is also found—and feared—in coal mines (*firedamp*), and it occurs as a product of decaying plant debris in swampy places (*marsh gas*). Pure methane for laboratory purposes is best prepared from methyl iodide, CH_3I , by the Grignard reaction (Sec. 7-17).

In the preceding chapter, methane was described as a typical nonpolar substance, with little attraction between different molecules but held together by *strong* covalent bonds *within* its molecules. The following more detailed description is entirely consistent with those statements. *The outstanding chemical properties of methane are its high stability and indifference toward most chemical agents.* In the absence of air it can be heated above 700°C with little change; but, in the temperature range 900 to 1100°C it is decomposed into its elements: $\text{CH}_4 \longrightarrow \text{C} + 2\text{H}_2$. Methane can be bubbled unchanged through concentrated solutions of acids and alkalis. The most active forms of combined oxygen, such as permanganate solutions, nitric acid, and dichromic acid, produce no noticeable effects. Unlike water, alcohol, and acids, the hydrogen atoms of methane are not displaced or affected by metallic sodium. The only exceptions to this general indifference which need be mentioned here are combustion and substitution by chlorine and bromine.

2-3 Combustion. From a jet, methane burns quietly in air or in oxygen with a hot nonluminous flame. Under some conditions, flame temperatures up to 1875°C have been measured. The same reaction occurs explosively when a mixture of methane (5 to 15 per cent) and air is ignited, as in certain coal-mine explosions. The equation for complete combustion is



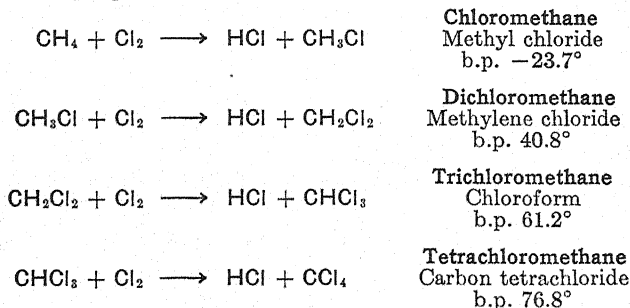
The major use of methane, as a component of natural gas for domestic and industrial fuel, depends upon the heat liberated when it burns.

2-4 Halogen Substitution. When methane mixed with chlorine gas is kept in the dark at ordinary temperatures, no change can be detected even on long standing. On exposure to light, or at temperatures above 250°C , reaction proceeds at rates which increase¹ with the intensity of the illumination, with the temperature, and in the presence of certain

† This is the *molecular* heat of combustion of methane; that is, it is the heat evolved in the complete combustion of 1 mole (gram-molecular weight), or 16 grams, of the substance. It will be recalled that the calorie (cal) is the quantity of heat required to raise the temperature of 1 gram of water 1°C . The more convenient kilogram-calorie (kcal) is 1000 times this quantity; it is also equal to 3.968 British thermal units (Btu).

¹ In direct sunlight or at quite high temperatures, mixtures of methane and chlorine in suitable proportions react explosively in the sense of the equation: $\text{CH}_4 + 2\text{Cl}_2 \longrightarrow \text{C} + 4\text{HCl}$.

catalysts. (The mechanism of photochlorination is discussed in Section 7.6.) The products are hydrogen chloride and a mixture of four organic compounds having the formulas CH_3Cl , CH_2Cl_2 , CHCl_3 , and CCl_4 . These products are formed in a succession of reactions described by the following equations:



It will be noted that for each chlorine atom which enters the organic molecule a hydrogen atom leaves simultaneously—as hydrogen chloride. This mode of reaction is known accordingly as *substitution* (*i.e.*, taking the place of), and the organic compounds formed are called methane *substitution products*.

Bromine reacts with methane in like manner, though more slowly than chlorine, to give HBr and a similar mixture of substitution products— CH_3Br , CH_2Br_2 , CHBr_3 , CBr_4 . Fluorine reacts explosively and iodine not at all.

A mixture of substitution products always results when methane is chlorinated or brominated. Long before all the CH_4 molecules are converted into CH_3Cl , some of the latter react with chlorine to form CH_2Cl_2 ; in like manner, certain amounts of CHCl_3 and CCl_4 appear while unchanged methane is still present. Hence, this is not a useful laboratory reaction. Chlorination of methane is used industrially to produce considerable quantities of methyl chloride and methylene chloride; methane is kept in large excess to cut down the formation of higher substitution products, and CH_3Cl and CH_2Cl_2 can be separated rather easily by distillation because of the spread of about 64 degrees in their boiling points.

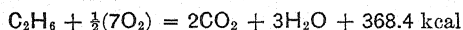
Chloroform and carbon tetrachloride are manufactured by indirect methods, as are also iodine and fluorine substitution products such as CH_3I and CCl_2F_2 (Secs. 15-9ff).

Tests for Substitution. When chlorine or bromine reacts by substitution with methane and other hydrocarbons, the hydrogen atoms removed from the organic molecules always appear as HCl or HBr (*never* as free hydrogen). Hence, the detection of one of these acid gases is reliable evidence of reaction by substitution. Traces

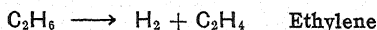
can be detected by their action on a strip of moist blue litmus paper or on a drop of silver nitrate solution suspended on the end of a stirring rod. Larger amounts may be recognized by the cloud of condensed moisture that is formed when the breath is blown across the mouth of any vessel containing one of these gases.

The very *slow* disappearance of the red color of bromine is a further indication that this halogen is reacting by substitution; its *addition* reactions with ethylene and most other unsaturated compounds are much faster, and the color of bromine usually disappears within the time required for mixing.

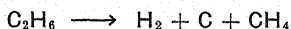
2-5 Ethane, C_2H_6 , is another hydrocarbon found in natural gas. It liquefies at $-88.6^\circ C$ and solidifies at $-183.2^\circ C$. Like methane it is colorless and odorless, practically insoluble in water, more soluble in acetone and ether, and a nonconductor of electricity. Ethane also resembles methane in stability, inertness, and general indifference to chemical reagents. It reacts like methane with chlorine and with bromine to give HCl or HBr and mixtures of substitution products such as C_2H_5Br , $C_2H_4Br_2$, etc. It burns in air, the equation for complete combustion being



Ethane is somewhat less resistant to heat than is methane. At around $500^\circ C$ (or lower, in the presence of certain catalysts) it begins to decompose in the sense of the equation

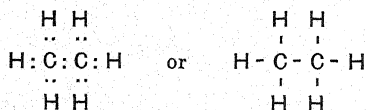


This reaction of *dehydrogenation* is used in the manufacture of ethylene. At somewhat higher temperatures there sets in a competing decomposition



Any reaction, like this one, in which a carbon-to-carbon bond is broken by heat is commonly described as *cracking*.

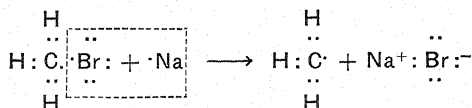
2-6 Synthesis of Ethane; Free Radicals. The structure of ethane, as represented in Figure 1-7 and by the formula



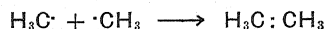
is the only one possible if the carbon and hydrogen atoms exert their normal valences of four and one. Direct proof of this structure and, specifically, that the two carbon atoms are joined together is furnished by the following synthesis. If bromomethane (methyl bromide, CH_3Br) is heated in a sealed tube with sodium, the metal becomes coated with a crystalline solid readily identified as sodium bromide. The other reaction product found in the tube is a gas which contains no halogen and

liquefies at -88.6°C . This product has the formula C_2H_6 , and careful comparison shows that it is identical in all physical and chemical properties with *ethane* as isolated from natural gas.

The course of the reaction can be explained as follows. The strongly electropositive sodium abstracts bromine atoms from the molecules of CH_3Br and thus forms the sodium bromide found. The immediate organic product is most probably a methyl *free radical*, $\text{H}_3\text{C}\cdot$, in which the carbon atom has an odd—unpaired—electron:



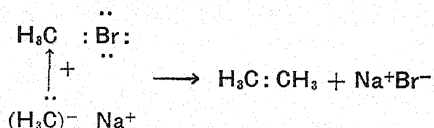
All the evidence indicates that such free radicals are highly reactive and that, almost as fast as formed, they unite by pairing electrons:



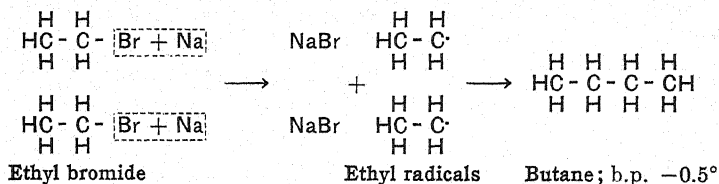
The resulting molecule of ethane is stable because each carbon atom has regained a complete octet. *The distinguishing feature of a free radical is an unpaired electron.*

2.7 The assumption that methyl and ethyl free radicals have real, though brief, existence goes far back into the history of organic chemistry. Actual proof is much more recent. In 1929 Paneth heated tetramethyllead, $(\text{CH}_3)_4\text{Pb}$, under diminished pressure and obtained evidence of $\cdot\text{CH}_3$ free radicals by their action on metallic mirrors placed some centimeters distant from the point of possible origin. Later, by heating $(\text{C}_2\text{H}_5)_4\text{Pb}$, he was able to detect $\cdot\text{C}_2\text{H}_5$ free radicals in like manner. Still more recently, methyl and ethyl radicals have been detected as momentary products of a modified Wurtz-Fittig reaction, consisting in the action of sodium *vapor* on gaseous CH_3Br and $\text{C}_2\text{H}_5\text{Br}$. The half-life period of simple free radicals such as these has been calculated as of the order of 0.006 second. Some complex free radicals, capable of prolonged existence, are described in Sections 22.18ff.

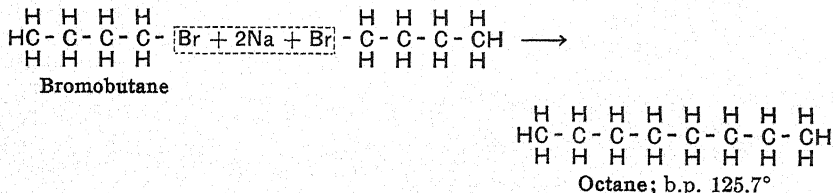
It is now recognized that short-lived free radicals are intermediates in many organic reactions such as oxidations, most polymerizations, and in general those which are catalyzed by light and by organic peroxides. It must not be assumed, however, in the absence of good evidence, that when a group of atoms passes unchanged from one compound to another it necessarily exists as a free radical at some stage of the process. As a matter of fact, some chemists still question the free-radical mechanism of the Wurtz-Fittig reaction as it is ordinarily conducted in the laboratory. They point out that sodium is able to react with H_3CBr to give methylsodium, $\text{Na}^+(\text{:CH}_3)^-$, and hold that the latter reacts with more methyl bromide to give the ethane which is formed:



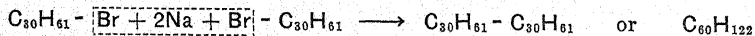
2.8 Carbon Chains; Wurtz-Fittig Synthesis. The atoms of carbon possess—to a degree which is not even approached by those of any other element—the ability to unite covalently with one another to form *carbon chains*. The over-all result of the action of sodium on CH_3Br is the formation of a *two-carbon* chain. The reaction is an example of one general laboratory method, known as the *Wurtz-Fittig synthesis*, for building up longer and longer chains. As a further example, sodium reacts with bromoethane (ethyl bromide, $\text{C}_2\text{H}_5\text{Br}$) to give the hydrocarbon butane, containing a *four-carbon* chain. Presumably, sodium liberates *ethyl* free radicals which immediately react by pairing their odd electrons:



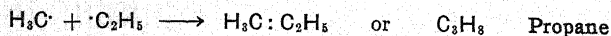
In like manner bromobutane (butyl bromide) yields *octane*, containing an *eight-carbon* chain:



As a final example of the wide applicability of this method, it may be noted that a hydrocarbon containing 60 carbon atoms, with a molecular weight of 842, has been obtained by the action of sodium on the compound $\text{C}_{30}\text{H}_{61}\text{Br}$:



2.9 In practice the Wurtz-Fittig synthesis is usually limited to the preparation of hydrocarbons containing an *even* number of carbon atoms. To obtain one with an *odd* number, it would be necessary to react sodium with a mixture of two different halogen compounds, such as CH_3Br and $\text{C}_2\text{H}_5\text{Br}$. This does indeed yield a certain amount of the three-carbon propane, by the union of methyl and ethyl free radicals:



But the product is mixed with approximately equal amounts of ethane and butane, formed by the reactions



It is impossible to separate such a mixture of gases in laboratory equipment.

HOMOLOGY

2-10 Alkanes; Paraffin Hydrocarbons. Methane, ethane, and the other hydrocarbons mentioned above are a few members of a large family of closely related compounds, known collectively as *alkanes* or *paraffin* hydrocarbons. This family includes many hydrocarbons with *normal* or unbranched chains (Table 2-1), which will be described first, and many others of branched-chain structure (Secs. 2-15ff). Enormous quantities of many of them occur in natural gas and petroleum, and from these complex mixtures a few individual hydrocarbons are now isolated in large amounts and relatively pure condition and are used in the manufacture of other organic compounds. Pure specimens can be made in the laboratory by the Wurtz-Fittig synthesis or by other general methods to be described later.

TABLE 2-1 SOME NORMAL SATURATED HYDROCARBONS

Formula	Name	Melting point, °C	Boiling point, °C†	Density†
CH ₄	Methane	-182.5	-161.5	0.4240 (at b.p.)
C ₂ H ₆	Ethane	-183.2	-88.6	0.5462 (at b.p.)
C ₃ H ₈	Propane	-187.7	-42.1	0.5824 (at b.p.)
C ₄ H ₁₀	<i>n</i> -Butane	-138.3	-0.5	0.6017 (at b.p.)
C ₅ H ₁₂	<i>n</i> -Pentane	-129.7	36.1	0.6262
C ₆ H ₁₄	<i>n</i> -Hexane	-95.3	68.7	0.6594
C ₇ H ₁₆	<i>n</i> -Heptane	-90.6	98.4	0.6837
C ₈ H ₁₈	<i>n</i> -Octane	-56.8	125.7	0.7026
C ₉ H ₂₀	<i>n</i> -Nonane	-53.6	150.8	0.7177
C ₁₀ H ₂₂	<i>n</i> -Decane	-29.7	174.0	0.7299
C ₁₁ H ₂₄	<i>n</i> -Undecane	-25.6	195.8	0.7404
C ₁₂ H ₂₆	<i>n</i> -Dodecane	-9.65	216.2	0.7493
C ₁₆ H ₃₄	<i>n</i> -Hexadecane	18.1	287.5	0.7749
C ₁₈ H ₃₈	<i>n</i> -Octadecane	28.0	308	0.7767 (at m.p.)
C ₂₀ H ₄₂	<i>n</i> -Eicosane	36.4	205.0 (15 mm)	0.7777 (at m.p.)
C ₃₀ H ₆₂	<i>n</i> -Triacontane	66	304 (15 mm)	0.7797 (at m.p.)

† Boiling points are for 760 mm pressure and density at $\frac{20}{4}^{\circ}$ except as noted.

The names of the first four members of the family—methane, ethane, propane, and butane—have come down from the early days of organic chemistry and give no clues to the formulas. (These can and should be memorized promptly.) Beginning with C₅ the names are formed systematically by adding the termination *-ane* to the stem of a numeral (usually of Greek but sometimes of Latin origin) which indicates the number of carbon atoms; *e.g.*, C₅H₁₂ is *pentane* (as in pentagon), C₈H₁₈ is *octane* (as in octet).

The number of hydrogen atoms in the formula of any alkane is given by the *general formula* C_nH_{2n+2} , which expresses the composition of every hydrocarbon of this family. This formula means that if there are n carbon atoms in any paraffin hydrocarbon it must contain twice that many hydrogen atoms, *plus two more*. The origin of this relation is apparent when we write the formula of any member in fully expanded form, *e.g.*, as was done for octane in Section 2·8.

2·11 Physical Properties. Reference to Table 2·1 shows that the melting points and boiling points of the normal alkanes rise progressively and somewhat regularly with the increasing number of carbon atoms (compare also Fig. 8·1, page 140). Summarizing in words some of the other information which the table gives in figures:

Methane, ethane, propane, and butane are all *gases* under ordinary conditions, but butane (b.p. -0.5°C) is easily liquefied. The hydrocarbons from pentane, C_5H_{12} (b.p. 36.1°C), to hexadecane, $C_{16}H_{34}$ (b.p. 287.5°C), are *liquids* with steadily increasing boiling points. Hexadecane forms a pasty solid when slightly chilled; *pure* specimens of higher members are *solid* at room temperature. Commencing at about C_{20} , boiling points are so high that these hydrocarbons cannot be distilled without decomposition except under reduced pressure. Density increases up to about C_{10} , after which the change is slight; all are lighter than water.

Solubility Relations. The familiar observation that gasoline, kerosene, and similar hydrocarbon mixtures are immiscible with water ("oil and water won't mix") is a useful reminder of the fact that *all* hydrocarbons are practically insoluble in water and water solutions. They are freely miscible with ether, acetone, carbon tetrachloride, and many other organic liquids; gasoline and other mixtures of low-boiling hydrocarbons are good solvents for fats, oils, and similar substances.

2·12 Chemical Properties. The normal alkanes are the least reactive of all organic compounds. Their general indifference toward chemical agents explains the origin of the alternate family name *paraffin*, meaning little affinity (L., *parum* + *affinis*). This self-satisfied nature has also earned them the name *saturated*—a term that will carry more meaning after a comparison with the *unsaturated* hydrocarbons (Chap. 3), which react by *addition*. Saturated hydrocarbons never *add* anything—a consequence of the fact that all electrons in their molecules are paired and all valence electrons are fully *shared* in strong covalent bonds. They do not reduce permanganate solutions; they do not dissolve in cold sulfuric acid and are unaffected by it; they react with chlorine and bromine by substitution only. Aside from the reactions mentioned below, the major exceptions to the rule of general inertness are certain *high-temperature* reactions—cracking, dehydrogenation, etc.—which are

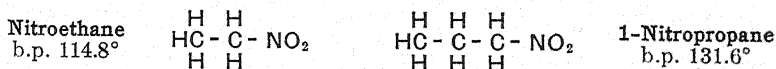
of great importance in the modern petroleum industry. These are considered in Chapter 6.

Combustion. When heated to their kindling temperatures with adequate air or oxygen, all hydrocarbons burn completely to carbon dioxide and water with maximum evolution of heat (though not necessarily maximum power in an engine). Reduced air supply results in incomplete combustion with carbon and carbon monoxide among the products. From the economic and industrial standpoints, combustion is by far the most important reaction of the paraffins because the energy thus made available is responsible for the value of enormous quantities of fuels—natural gas, gasoline, fuel oil, etc.—composed mainly of these hydrocarbons. Molar heats of (complete) combustion increase regularly with the size of the molecule in the paraffin family and are but little affected by chain branching (Sec. 2·15). The average increment for each CH_2 group (*i.e.*, 12 grams of carbon and 2 grams of hydrogen) is 157 kcal.

The *controlled* oxidation of hydrocarbons to obtain other organic compounds is discussed in Section 6·19.

Halogenation. The industrial chlorination of methane to produce methyl chloride and methylene chloride has been mentioned. This reaction is being used increasingly with other paraffin hydrocarbons for the manufacture of *mono* chlorides, by keeping the hydrocarbon in large excess over chlorine. An important example is the chlorination of a mixture of pentane and isopentane (Sec. 7·5). So far as concerns *laboratory* syntheses, any method involving the direct chlorination or bromination of a saturated aliphatic hydrocarbon must be regarded as impracticable; the reactions cannot be controlled effectively, and the resulting mixtures are too hard to separate. Fluorination is discussed in Section 15·15.

Nitration. The gaseous paraffin hydrocarbons are hardly affected by bubbling through boiling nitric acid or mixtures of nitric and sulfuric acid. But at about 400°C ethane, propane, and butane react with the vapors of nitric acid to give substitution products called *nitroparaffins* or *nitroalkanes*; *e.g.*,



This process of *vapor-phase nitration* has now made available commercial quantities of nitro derivatives of methane, ethane, propane, and butane. The reaction is not a simple substitution as would be suggested by the equation



because with propane, for example, it yields also considerable quantities of nitromethane and nitroethane. As a matter of fact, most of the $\text{H}_3\text{C}\cdot\text{NO}_2$ produced and sold is obtained as a by-product in nitrating propane. Methane itself does not react appreciably at 400°C , and even at 475°C the yield of $\text{H}_3\text{C}\cdot\text{NO}_2$ is poor. This is further evidence of the special stability of the methane molecule.

The exact course of the gas-phase nitration reaction is not entirely clear. At the nitrating temperatures, HNO_3 is dissociated into water and nitrogen dioxide, NO_2 . The latter is one of the few known molecules which contains an *odd* number (23) of electrons. This means that one electron cannot be paired and the molecule is therefore, essentially, a free radical. One widely held theory is that, under the conditions used, the hydrocarbons are split into all the different free radicals which can result from breaking *any* C:H or C:C bond. If this indeed occurs (as is strongly suggested by the mixtures of nitro compounds regularly obtained), it is easy to see how these organic free radicals could unite readily with nitrogen dioxide molecules by pairing odd electrons.

Beginning with pentane, the alkanes can be nitrated in the liquid phase by prolonged heating with a mixture of nitric and sulfuric acids. This is accompanied by considerable oxidation, and the reaction is of only minor importance in comparison with its use in the aromatic series (Sec. 5-10).

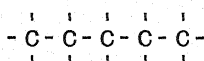
2-13 Homology. What we have been calling the *family* of alkanes or paraffin hydrocarbons is known in organic chemistry as a *homologous series* (Gr., *homos*, similar), and all the members of such a series are called *homologues* of one another. The distinguishing characteristics of every such series may be summarized as follows: (1) All members of a homologous series have a *similar structure*; e.g., the structure characteristic of all the paraffin hydrocarbons is a *saturated open chain*. (2) Because of this similarity in structure, the members of a homologous series have similar chemical properties and can be made by *general methods*. (3) The composition of all the members of a homologous series can be expressed by a *general formula*. (4) Successive members always differ in composition by CH_2 and in molecular weight by 14; *any* two members differ by some multiple of CH_2 . (5) Physical properties of homologues change progressively and somewhat regularly with the number of carbon atoms.

The importance of homology in organic chemistry can hardly be overestimated. It is a basis of simplification through which great numbers of carbon compounds can be studied as families—i.e., as homologous series—rather than as individuals. This eliminates much detailed description, reduces memory work, and makes it possible to focus attention upon the essential *structures* which are responsible for common *properties*.

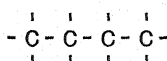
ISOMERISM; BRANCHED CARBON CHAINS; ISOALKANES

2-14 Ethane is the only known substance¹ composed of two carbon and six hydrogen atoms, and propane is the only one of the composition C_3H_8 . Hence it appears that these particular building materials (2C and 6H, 3C and 8H) can be put together in *one* stable arrangement only. But with larger numbers of atoms, two or more arrangements are possible. Thus there arise *different compounds composed of the same numbers of the same kinds of atoms*. Such compounds are called *isomers*, and this phenomenon is known as *isomerism*.

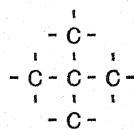
2-15 Chain Isomerism. In the hydrocarbons previously described, no carbon atom is joined to more than two others in forming the links of the chain. But a given carbon atom may use three—or all four—of its valence electrons in forming covalent bonds with other carbon atoms. In this way, the same number of carbon atoms may be combined in more than one arrangement, *e.g.*,



(I)



(II)



(III)

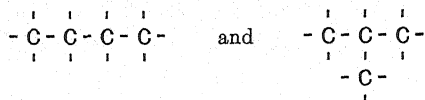
Such differences in chain structure furnish one of the commonest sources of isomerism.

Nomenclature. Carbon chains such as those in (II) and (III) are called *branched*, in distinction from the *normal* chains already considered. Carbon atoms are described as *secondary*, *tertiary*, and *quaternary* when two, three, and four other carbon atoms, respectively, are directly attached; a *primary* carbon atom has *not more than one* other carbon directly attached.

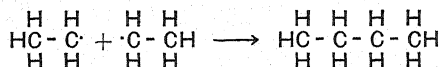
2-16 Isomeric Butanes. Two hydrocarbons, each with the molecular formula C_4H_{10} , have been isolated from natural gas; one boils at -0.5°C and the other at -11.7°C . By the use of structural formulas, or models, it is easy to show that four carbon atoms can be joined in two—but only

¹ When we say that ethane is the *only* known compound of the composition C_2H_6 , we mean that all pure specimens of a substance having this composition are identical in every physical and chemical property. If two pure specimens of matter can be shown to differ, either in composition or in any physical or chemical property, they must be regarded as *different* substances.

two—different ways if the usual valence rules hold good and bonds are left for 10 hydrogen atoms:

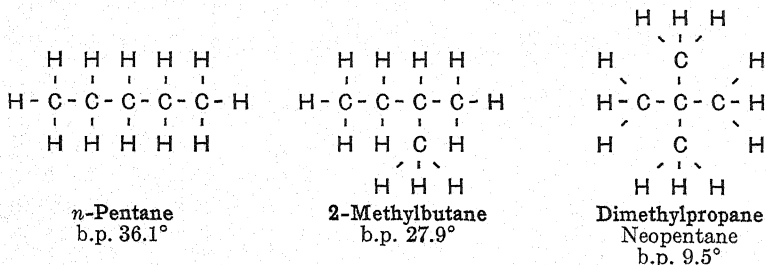


Adding the 10 hydrogen atoms gives two reasonable structures for these hydrocarbons—but this does not tell which structure belongs to either substance. That information is furnished by the fact that the butane obtained from ethyl bromide by the Wurtz-Fittig synthesis is the one which boils at -0.5°C . Since it is formed there by the union of two ethyl free radicals,



it must have the normal carbon chain. The alternate structure, $(\text{H}_3\text{C})_3\text{C}\cdot\text{H}$, is therefore assigned to the isomer which boils at -11.7°C . This compound is called isobutane.

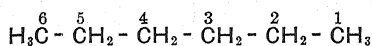
2-17 Isomeric Pentanes, C_5H_{12} . With five carbon atoms in the molecule there are possible¹ the three different chain structures shown in Section 2-15. Supplying in each of these the symbols for 12 hydrogen atoms gives three isomeric formulas, C_5H_{12} , as follows:



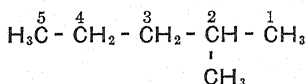
The three compounds represented by these formulas are all well known, and no other substance having the composition C_5H_{12} has ever been obtained. In other words, the number of known isomers agrees exactly with the prediction based on the structural theory.

2-18 Isomeric Hexanes. For compounds of the formula C_6H_{14} , five isomers, corresponding to five different chain structures, can be predicted. These five *hexanes* are all known. Their condensed structural formulas, boiling points, and individual names are as follows:

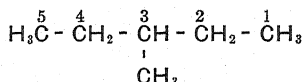
¹ Other structures, containing closed chains, are also possible and exist (Chap. 4) but do not leave the valences necessary for attaching all 12 hydrogen atoms.



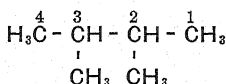
n-Hexane
b.p. 68.7°



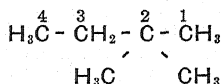
2-Methylpentane
b.p. 60.3°



3-Methylpentane
b.p. 63.3°



2,3-Dimethylbutane
b.p. 58.0°



2,2-Dimethylbutane
b.p. 49.7°

2.19 Isomeric Higher Alkanes; Isoalkanes. The possibilities for chain isomerism increase rapidly with the number of carbon atoms in organic molecules. For hydrocarbons of the formula $\text{C}_{10}\text{H}_{22}$, 75 different chain structures are possible¹; for $\text{C}_{15}\text{H}_{32}$, the number is 4,347; and for $\text{C}_{20}\text{H}_{42}$, it is 366,319! Only a few of the possible isomers higher than the octanes are known, but there appears no reason why any one, or all of them, might not be synthesized through the necessary expenditure of time and effort. Among the simpler compounds, where investigations are complete, the number known is equal to—and in no instance exceeds—that predicted by the structural theories of organic chemistry.

The branched-chain isomers of the normal alkanes are known collectively as *isoalkanes* or *isoparaffins*. Individual compounds are named as described below. The normal and isoalkanes belong to the same saturated open-chain homologous series (Sec. 2.13).

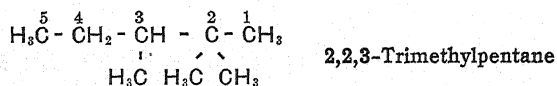
2.20 Names of Isomers. In order to avoid confusion in reference, it is important to give each known chemical compound a name that is distinctive and, so far as possible, descriptive of its structure. The following rules, designed to meet these requirements, are observed in naming isoalkanes:

1. Locate the longest unbranched, normal chain in the molecule.
2. Number the carbon atoms of this chain consecutively, beginning with the end nearest which a carbon *side chain*—usually a methyl group—is attached.
3. Name the compound as a substitution product of the normal alkane corresponding to the numbered chain (Table 2-1).
4. Indicate *how many* side chains, if more than one, by the appropriate prefix (*di-*, *tri-*, *tetra-*, *penta-*, etc.).

¹ Cf. *J. Am. Chem. Soc.*, **53**, 3042, 3077; **55**, 252, 680; **56**, 157.

5. Show the *position* or point of attachment of each side chain by the figures used in numbering the normal chain; each figure is repeated as many times as there are side chains.

The application of these rules is illustrated in the names of the isomeric pentanes and hexanes, above. As a further illustration, consider the more complicated hydrocarbon of the molecular formula C_8H_{18} (one of the isomeric octanes), having the following structure:



The longest unforked chain contains five carbon atoms, and the compound is therefore named as a derivative of *pentane*. The carbon atoms of this chain are numbered from 1 to 5, commencing at the end of the chain nearest which a methyl side chain is joined. Two methyl groups are attached to carbon number 2, and one methyl group is attached to carbon number 3. The complete name is, therefore, *2,2,3-trimethylpentane*.

2-21 Systematic Nomenclature. The foregoing rules are part of the systematic method for naming organic compounds. This is often called the *Geneva system* because it originated at an international congress of chemists held in that city in 1892. Its purpose was to eliminate the confusion which was growing through the use of different names for the same compound. The system then proposed was never completed and has since been modified in various ways but remains the basis of today's systematic nomenclature. The currently accepted rules are sometimes referred to as the IUC system because they are sponsored by the International Union of Chemistry.¹

Because they are free from ambiguity, systematic names are used almost exclusively for complex compounds. But they often seem unnecessarily long for simple molecules. Partly for this reason and partly on account of traditional usage, simple substances frequently encountered are apt to be called by names which are shorter—even though they are not descriptive. For example, the forked-chain isomer of butane, methylpropane, is invariably called *isobutane* and the pentane $C(CH_3)_4$ is known as *neopentane* rather than dimethylpropane.

2-22 Chain Branching and Physical Properties. While every change in molecular architecture results in some change in physical properties, the effects of chain branching are minor ones. By comparing the five isomeric hexanes, above, it will be noted that the normal compound has the highest boiling point, 68.7°C, and the isomer with the most forked

¹ Useful summaries of the official rules, with explanations, may be found in the common "handbooks" of chemistry, usually just preceding the tables of organic compounds.

chain (2,2-dimethylbutane) has the lowest, 49.7°C. This illustrates a fairly general rule. But it should be noted further that the effect is relatively small in comparison with that of a change in molecular weight, as may be seen from the following:

	Molecular weight	Boiling point, °C
Lowest boiling heptane, C_7H_{16}	100	79.2
All hexanes, C_6H_{14}	86	49.7-68.7
Highest boiling pentane C_5H_{12}	72	36.1

The melting points of organic compounds are often more affected by small changes in structure than are the boiling points, but the effect is even less predictable. One may cite the fact that neopentane, $C(CH_3)_4$, melts at a temperature more than a hundred degrees higher than either of its isomers. But this is probably less an effect of chain branching as such than of the high *symmetry* of this molecule. It is often observed that molecules which are compact and, especially, those which are highly symmetrical have higher melting points than their isomers. This fact is interpreted to mean that such molecules lend themselves better to the building of a crystal lattice in which intermolecular attractions are relatively strong (or, as someone has expressed it, highly symmetrical molecules can more readily "sit down").

2·23 Chain Branching and Chemical Properties. The isoalkanes resemble their normal isomers in the chemical properties described in Section 2·12, with two important exceptions. One chemical effect of chain branching, of interest to the general public, is a difference in the rate of combustion, which determines the "knock" or "antiknock" quality of a motor fuel. The normal alkanes, such as *n*-heptane and *n*-octane, produce engine knock readily, while some of their highly branched isomers show excellent antiknock performance (Sec. 6·7).

The other noteworthy property found among the isoalkanes is the special reactivity of hydrogen when joined to a *tertiary* carbon atom as in isobutane, $(H_3C)_3CH$, and other hydrocarbons of the type structure R_3CH .† A hydrogen atom thus attached is more easily replaced by the action of chlorine or of nitric acid; it will react with certain chemicals, such as chlorosulfonic acid and antimony pentachloride, which have little effect on normal alkanes; it can be replaced by deuterium (heavy hydrogen) when treated with heavy sulfuric acid, D_2SO_4 . Hydrocarbons containing the grouping R_3CH are rather easily oxidized and so are

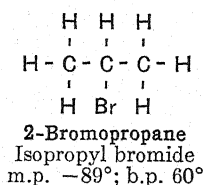
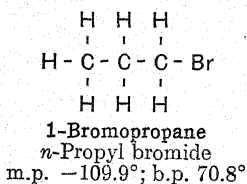
† R is a conventional symbol used to indicate *any* hydrocarbon group or radical such as CH_3 , C_2H_5 , etc. (Sec. 2·24).

capable of reducing permanganate solutions; the initial product is probably the alcohol $R_3C.OH$, but reaction proceeds farther. Finally, it should be noted that this special reactivity enables hydrocarbons of the type R_3CH to take part in the important industrial reaction known as *alkylation*, which is used in the production of high-quality motor fuels (Sec. 6·10).

2·24 Alkyl Groups and Radicals. The class name *alkane* for the C_nH_{2n+2} hydrocarbons was formed by combining the word *alkyl* with the distinguishing termination *-ane*. The group of atoms which remains if a hydrogen atom is removed—or is imagined as removed—from any one of these hydrocarbons is called an alkyl¹ group or radical. Individually, these are named after the parent hydrocarbons by changing *-ane* to *-yl*; e.g., CH_3 , *methyl*, from *methane*; C_4H_9 , *butyl*, from *butane*, etc.

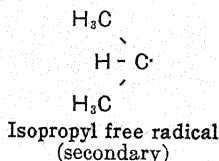
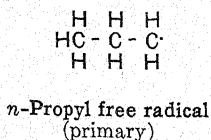
These terms are often useful in forming the names of other organic compounds and in describing reactions in which groups of atoms are transferred—apparently unchanged within themselves—from one compound to another. Long before the existence of *free* radicals was demonstrated, such groups of atoms came to be called radicals (following a common use of that term in mathematics), and the practice still continues. Confusion can be avoided by taking care to include the adjective *free* when that special meaning is intended.

2·25 Position Isomers; Isomeric Radicals. There are two isomers of the composition C_3H_7Br which, from their relations to other compounds, are known to have the following structures:



These are called *position* isomers since their difference lies only in the position of the bromine atom on the same three-carbon chain.

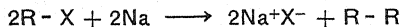
These bromides can give rise to free radicals (e.g., when treated with sodium) in which the unpaired electron belongs to a primary or to a secondary carbon atom, respectively:



¹ Cf. footnote page 119.

Similarly, in naming compounds containing a C_3H_7 group, the terms *n*-propyl and isopropyl are used to indicate whether the union is through a primary or a secondary carbon atom, *e.g.*, *n*-propyl alcohol, $H_3C.CH_2-CH_2(OH)$, and isopropyl alcohol, $H_3C.CH(OH).CH_3$.

2-26 General Reactions; Type Equations. Reactions such as the Wurtz-Fittig synthesis, which are common to many compounds of a like nature, often serve as *general* methods of preparation. It is convenient to express them by conventional symbols in *type* equations. Using R to signify a hydrocarbon radical and X (or Hal) as a symbol for one atom of a halogen—F, Cl, Br, I—any compound of the nature of CH_3Br and C_2H_5Cl may be represented by RX . The type equation



thus gives a generalized statement of the Wurtz-Fittig reaction.

Questions

1. The inflammable bubbles of marsh gas, sometimes seen rising from swamp water, are composed chiefly of methane. (a) What solubility relation of methane is illustrated? (b) How can this property be applied in the laboratory to filling a bottle with methane without admixture with air?

2. (a) What chemical property of methane is illustrated by the use of natural gas in the laboratory? (b) What is unusual in the fact that sodium does not displace hydrogen from methane?

3. Write structural equations for the formation of four organic compounds by the action of bromine on methane, and name them by analogy to the chlorine substitution products.

4. In what way does the *substitution* of hydrogen by halogen when chlorine acts on methane differ from the *displacement* of hydrogen when sodium acts on water?

5. Describe in detail the tests and the observations that would lead you to conclude that a gaseous hydrocarbon was reacting with bromine by substitution.

6. Distinguish between the terms "dehydrogenation" and "cracking."

7. (a) Explain the principle of the Wurtz-Fittig synthesis. (b) Define the term *methyl free radical*, and explain why its actual existence was so difficult to prove. (c) Assuming that a covalent linkage between the atoms X and Y might be severed in each of the following ways, describe accurately the nature of each of the possible products $X\vdots Y$, $X\cdot\cdot Y$, $X\vdash Y$.

8. A mixture of one mole each of $CH_3.CH_2.Br$ and $CH_3.CH_2.CH_2.Br$ is heated with metallic sodium. Write structural equations for the formation of the three organic products to be expected and name them.

9. Selecting several specific examples from Table 2-1, show that any two alkanes differ in their molecular formulas by CH_2 or some multiple of CH_2 .

10. Summarize the relations among the physical properties of the alkanes. On what do the differences seem to depend?

11. Butane is a gas under ordinary conditions. By what changes in conditions can it be liquefied?

12. Describe the appearance of the pure hydrocarbon $C_{22}H_{46}$ at room temperature (cf. Table 2-1). If a little of this hydrocarbon were shaken with water, would it dis-

solve? Would it float or sink? What would happen if you attempted to distill it under the conditions ordinarily used for distilling *n*-octane?

13. Summarize the general chemical properties of the normal alkanes.

14. Write the balanced equation for the complete combustion of propane and calculate its approximate (molar) heat of combustion from information given in this chapter.

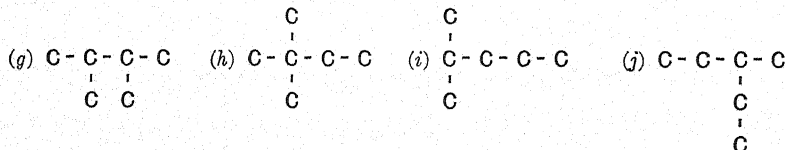
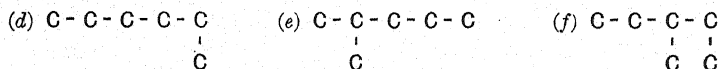
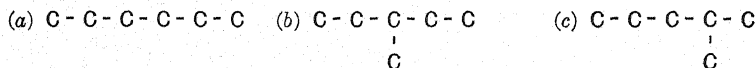
15. Assume that in gas-phase nitration at 375°C propane yields all the free radicals that can be imagined by breaking *any* C:H or C:C bond. Write the structural formulas of all the mononitro compounds which could be formed.

16. Summarize the characteristics of a homologous series.

17. (a) Define "isomers" and "isomerism." (b) Give examples of and define "position isomers" and "chain isomers." (c) What is the relation, if any, between the molecular weights of isomeric compounds?

18. Explain clearly how the method of synthesis described in Section 2-8 proves that the butane boiling at -0.5°C , found in natural gas, has the normal chain structure.

19. Indicate which of the following formulas represent different chain structures and which are duplicates:



20. Write out the structural formulas and the systematic names of all the possible heptanes, C_7H_{16} , and hand to the instructor at the time designated. Be prepared to indicate all tertiary and quaternary carbon atoms.

21. Write structural equations for the reactions to be expected if each of the following compounds were heated with sodium and give the systematic names of the products: (a) 1-bromopropane; (b) 2-bromopropane; (c) 2-bromobutane; (d) 1-bromo-2-methylbutane.

22. Classify the compounds formed in question 21 on the basis of: (a) their probable quality as antiknock fuels, and (b) any probable difference in chemical reactivity.

23. Name the normal primary alkyl radicals derived from the first six paraffin hydrocarbons.

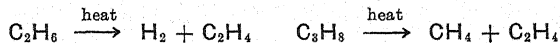
CHAPTER 3

UNSATURATION; DOUBLE AND TRIPLE BONDS

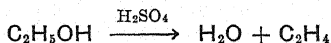
Many hydrocarbons are known which differ from the alkanes in that they react by addition. These are described collectively as *unsaturated* hydrocarbons. They include several homologous series. Ethylene is the simplest member of the most extensive series of unsaturated aliphatic hydrocarbons, called alkenes or olefins. Acetylene and butadiene are the outstanding representatives of two other series.

ALKENES OR OLEFINS

3.1 Ethylene, C_2H_4 , is a gas (b.p. $-103.7^\circ C$) of somewhat sweetish odor which burns with a luminous flame. It is a common product when organic matter is heated in the absence of air, and this is its origin in the gases from coke ovens and petroleum cracking units, where it is available in huge quantities. Ethylene is also produced industrially by dehydrogenating ethane and by cracking propane:



It is usually prepared in the laboratory by heating ethyl alcohol with a dehydrating acid such as sulfuric:



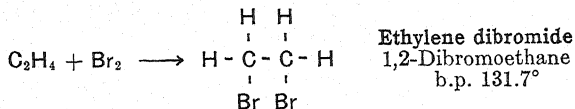
Ethylene is used to some extent as a general anesthetic and to hasten the ripening of citrus fruits. Enormously greater amounts are consumed in the production of other organic compounds by methods which depend upon its high chemical reactivity—especially, its ability to react by addition.

It will be recalled that methane and ethane react with bromine slowly and by a *substitution* reaction which requires the aid of either light or a high temperature. Ethylene on the contrary decolorizes bromine vapors quickly at room temperature, either in light or in darkness, and forms an *addition* product as summarized by the equation

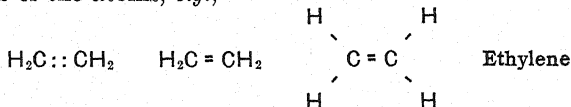


This ability to *add* something to the molecule is the outstanding characteristic of all *unsaturated* compounds.

3.2 Double Bonds. The chemical behavior of the compound $C_2H_4Br_2$ obtained from ethylene shows clearly that in its formation one bromine atom has become attached to *each* carbon:



Hence, it must be concluded that neither carbon atom in the original ethylene had all its combining power fully satisfied. This condition of unsaturation is ascribed to a *double bond*—a type of covalent linkage in which *atoms share two pairs of electrons*. The double bond is usually represented in formulas by two pairs of dots or two parallel lines between the symbols of the atoms, *e.g.*,



When necessary to distinguish it from other double bonds (*e.g.*, $C=O$), this type of linkage between *carbon* atoms is referred to as the *ethylenic* double bond.

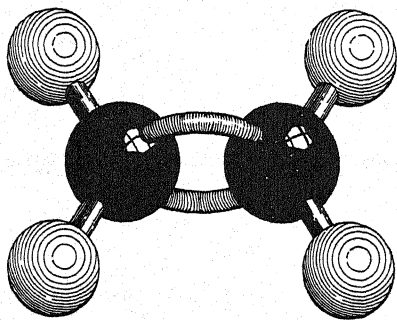


FIG. 3-1 Model representing the ethylene molecule, C_2H_4 . This suggests the established fact that the six atoms lie in a plane. It is unsatisfactory in failing to suggest any difference between the two linkages that constitute a double bond.

The two shared pairs of electrons which form a double bond are unlike both in their average positions and in their behavior. The most probable position of one pair is in or near the line between the carbon nuclei, just as in a single bond. The *unsaturation* or π (*pi*) electrons, which form the other bond, are under less constraint and are apt to be found much farther away (one above and one below the plane which contains the carbon atoms and the other atoms or groups joined directly to them;

cf. Figure 3-1). Hence, the unsaturation electrons are more easily polarized (Sec. 3-8) and more available for reactions with other substances.

Physical evidence shows distinct differences between double and single bonds. We know from X-ray and electron-diffraction measurements that when atoms are joined by a double bond the distance between their

centers is shorter than for a single bond. This distance is 1.34 Å for the C=C bond in ethylene as against 1.54 Å for the C—C bond of ethane. Values very close to these have been found also in many other compounds of the two types. We know also from thermochemical and spectroscopic data that the bond energies¹ differ widely—151 kcal for the double bond, C=C, as against 84 kcal for the single bond. The difference of about 67 kcal is a measure of the additional binding force exerted by the unsaturation electrons.

3-3 Homologues of Ethylene. Ethylene and the other unsaturated hydrocarbons containing *one* double bond form the homologous series of *alkenes* or *olefins*, within which the usual relations prevail (Sec. 2-13). Owing to the presence of the double bond, each alkene contains two less hydrogen atoms than the corresponding² alkane, and the general formula is C_nH_{2n} .

The lower alkenes seldom occur in nature, either in natural gas, crude petroleum, or elsewhere. Their chief source is the dehydrogenation or the cracking of other organic compounds, particularly in petroleum refining where enormous quantities are produced (Chap. 6). Chemical interest centers mainly in the gaseous alkenes—ethylene, propene, and the butenes. These enter into the large-scale production of synthetic rubber, plastics, high-octane gasoline, alcohols, and a large number of other organic compounds. Laboratory methods for making alkenes are described below.

The presence of the double bond has relatively little effect on *physical* properties; corresponding alkanes and alkenes of similar chain structures do not differ greatly in their boiling points, melting points, or densities. Insolubility in water and greater solubility in organic liquids such as acetone are characteristic of both series—and indeed of *all* series of hydrocarbons.

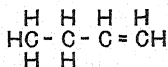
The outstanding *chemical* properties of the alkenes are their many *addition* reactions and the ease with which they are oxidized, as described later in this chapter.

3-4 Isomerism and Nomenclature. Corresponding to the two butanes there are three³ isomeric butenes, C_4H_8 :

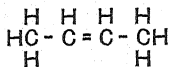
¹ Bond energy may be defined as the amount of energy required to break a particular bond (that is, to separate completely the atoms that were joined by this bond) in one mole of a substance (6×10^{23} molecules). The values given are calculated for the gaseous state.

² Compounds of different series are described as *corresponding* when they contain the same number of carbon atoms.

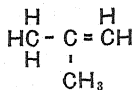
³ Actually, there are four. The difference between the *cis* and *trans* forms of 2-butene is explained in Section 15-24.



1-Butene
b.p. -6.3°



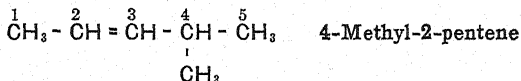
2-Butene
b.p. -3.7°



Isobutene; isobutylene
Methylpropene
b.p. -6.9°

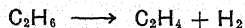
Isobutene has the branched-chain structure of isobutane; both the others contain the unbranched chain of normal butane and differ only in the position of the double bond. Similar opportunities for chain and position isomerism occur and are more numerous among the higher alkenes; for example, 13 hexenes, C_6H_{12} , are possible as compared with five hexanes (Sec. 2-18).

Nomenclature. The systematic names of the alkenes are formed from those of the corresponding alkanes by changing the terminal *-ane* to *-ene*; e.g., a C_5H_{10} alkene is a pentene and C_6H_{12} is a hexene. Numbering of the chain begins with the end nearest which the double bond occurs,¹ and the position of the double bond is indicated by the smaller of the two numbers referring to the carbon atoms which it joins; e.g.,



The simpler and commoner members are generally called by names which are older than the Geneva system, as follows: *ethylene*, for ethene, C_2H_4 ; *propylene*, for propene, C_3H_6 ; *isobutene* or *isobutylene* for methylpropene, C_4H_8 ; the pentenes, C_5H_{10} , are often called *amylenes*.

3-5 Forming Double Bonds. The principle of the general method for forming an ethylenic double bond is the removal of an atom or group from each of two carbon atoms already joined by a single bond. The reagents and conditions necessary to do this depend upon the nature of the starting material. Industrially, the raw material is ordinarily a saturated hydrocarbon which may be *dehydrogenated* by heat, often with the aid of a catalyst, e.g.,

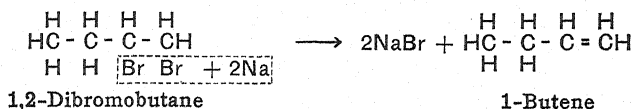


(The *cracking* of hydrocarbons, described in Section 6-4, is a more important industrial source.) In the laboratory the starting material is usually either a halogen compound or an alcohol.

¹ In the original Geneva system (which is used in Beilstein's "Handbuch der organischen Chemie") the numbering begins with the end nearest which a *methyl* group occurs (as with the alkanes, Sec. 2-20), and the hexene shown above is listed there as 2-methyl-penten-(3).

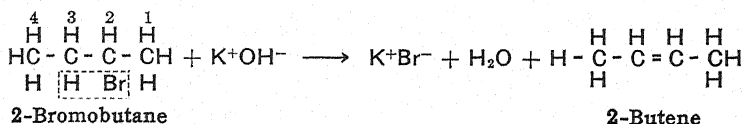
The more modern IUC system is based on giving the lowest possible number to the *principal function*—that is, to the atom or group which is most important in connection with the chemical properties of the compound. In an alkene this is the double bond, and not a methyl side chain.

3-6 Formation from Halides. An alkene can be prepared from a compound containing two atoms of halogen attached to adjacent carbon atoms by heating with metallic zinc or sodium, *e.g.*,



This is something like an internal Wurtz-Fittig reaction. The method is not used widely because the necessary dihalogen compounds are rarely available except as they have been prepared *from* the corresponding alkenes.

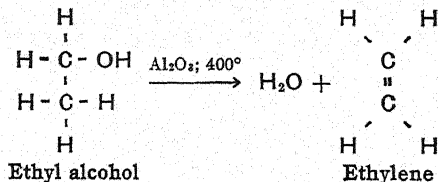
A more general method is the action of hot alkali on a monohalide. The usual laboratory reagent is a solution of potassium hydroxide in ethyl alcohol ("alcoholic KOH"), alcohol being used because it dissolves both reactants. The over-all effect is the elimination of the elements of a hydrogen halide (HCl, HBr, HI), *e.g.*,



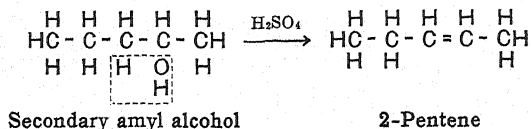
The principal product here is 2-butene, as shown; that is, the hydrogen atom comes from C³. It is mixed with a smaller amount of the isomer 1-butene, which is formed if the hydrogen atom comes from C¹. This larger yield of 2-butene illustrates a general rule that hydrogen is more easily removed from that adjacent carbon which has *fewer* hydrogen atoms in the beginning.

This method gives good yields of alkenes from alkyl halides in which the halogen atom is joined to a secondary or a tertiary carbon atom. It is less successful with primary halides (Sec. 7-12).

3-7 Alkenes from Alcohols. An alcohol is an organic compound containing the hydroxyl group, OH. If this group can be separated from carbon, along with a hydrogen atom from an adjoining carbon, a double bond is formed. The effect is the elimination of a molecule of water from a molecule of alcohol—*dehydration*. This may be accomplished by passing the vapor of the alcohol over a heated catalyst, *e.g.*,



The commoner method is to heat the liquid alcohol with a strong acid, usually sulfuric:

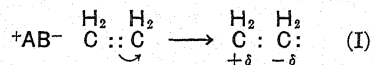


The product is mainly 2-pentene as indicated, with a much smaller amount of 1-pentene; thus, again, H is eliminated prevalingly from that adjacent carbon atom which is poorer in hydrogen.

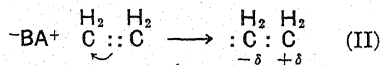
The dehydration of alcohols is the most general laboratory method for the preparation of alkenes (double bond formation). It is considered in more detail in Section 8·12.

3·8 Addition Reactions. Ethylene and other alkenes react by addition not only with chlorine and bromine but with many other substances. Before describing some of these reactions individually, it is important to consider the general mechanism through which all of them seem to take place. This is based upon the polarizability of the double bond.

We have seen (Sec. 1·9) why certain molecules are permanent dipoles. The term *polarizability* refers to a *temporary* displacement of electrons which may occur under particular conditions. Consider for example a molecule of ethylene which is approached closely by a highly polar molecule, $^+\text{AB}^-$, in the direction shown in (I). The electrons of the double bond would be repelled, and we may imagine the unsaturation pair as passing over very largely to the carbon atom at the right:



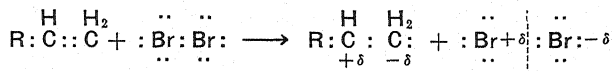
If the positive pole of $^+\text{AB}^-$ happened to approach the ethylene molecule, the unsaturation pair would be attracted and move to the left, as in (II):



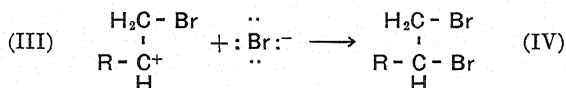
In either event the ethylene molecule would become polarized—but only temporarily, because the effect can last only as long as the $^+\text{AB}^-$ and $\text{H}_2\text{C}::\text{CH}_2$ molecules maintain their relative positions. Such a temporary polarization can be induced by a molecule or ion of a reagent or a solvent, or by a catalyst. The π electrons of a double bond, being under less restraint than a single-bond pair, are more polarizable by such external influence.¹

¹ In the *extreme* form which can be imagined as produced through the polarizability of a double bond, the π electrons must be regarded as having left the valence shell of

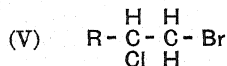
In the addition of bromine to an alkene it would appear that, as an initial step, molecules of the reactants *polarize each other*, somewhat as follows:



Next, the $+\delta$ bromine adds to the $-\delta$ carbon, forming the carbonium ion (III) and a bromide ion, Br^- . These combine quickly to form the dibromide (IV), which is the final reaction product:



Evidence that the two bromine atoms do not add in a single step includes the observation that, when the reaction takes place in a solution of Na^+Cl^- , there is formed not only (IV) but also the chloro-bromo addition product (V):



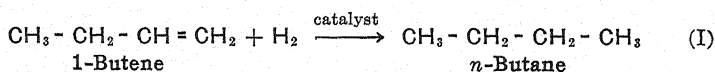
This indicates clearly a stepwise mechanism in which, once the carbonium ion (III) is formed by the attack of free bromine, it may combine with whatever negative ion it happens first to encounter.

It seems clear that many other alkene addition reactions begin with an attack on the unsaturation electrons of the double bond by some *electron-seeking* reagent. If the attack is successful, its immediate product is a carbonium ion.

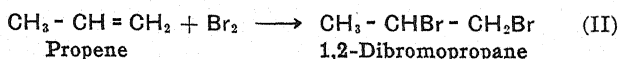
3.9 Carbonium Ions; Carbanions. When a proton, or another electron-deficient ion, adds at a $\text{C}::\text{C}$ bond, the unsaturation pair of electrons is used in binding this ion covalently to a carbon atom. Thus an electron pair, belonging in the valence shells of *two* carbon atoms of the alkene, passes completely and permanently into the shell of one of them. The other carbon atom is left with only six valence electrons—an “open sextet”—and the ion carries a unit positive charge. This is the distinguishing structure of a *carbonium ion*. We shall encounter other ways in which carbonium ions may be formed. One of these is in reac-

one carbon atom, passing completely into that of the other. (This is sometimes called an *electromeric displacement*.) Movement in *this direction* can lead to higher $-\delta$ and $+\delta$ charges within a molecule than those which result simply from induction by an electronegative atom (Sec. 1.9). This helps to explain the common observation that the polarizability of a molecule seems to be more important in determining its behavior than is its permanent polarization.

Addition of hydrogen, H_2 , requires the aid of a suitable catalyst and, usually, hydrogen under considerable pressure. The catalyst may be finely divided platinum ("platinum black"), which is often effective in the cold, or some form of finely divided nickel at higher temperatures. Raney nickel, a particularly active hydrogenation catalyst, is prepared by treating a nickel-aluminum alloy with warm sodium hydroxide; this dissolves out the aluminum and leaves the nickel with a large surface area and in a very active form. The product of hydrogenating an alkene is the corresponding alkane, *e.g.*,



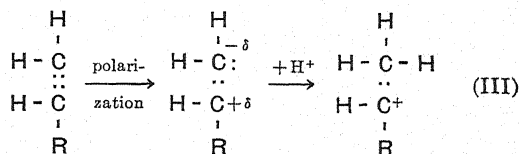
Addition of Halogens. Bromine and chlorine add readily, even in the dark, as already stated, *e.g.*,



The addition of iodine has been rarely if ever observed, but iodine monochloride, ICl , adds readily.

Bromine Test for Unsaturation. A convenient test for hydrocarbons containing the ethylenic double bond (and for other unsaturated compounds) is the *rapid* fading of the red-brown color of free bromine when the latter is added to the substance examined. The speed of this addition reaction prevents any confusion with the much slower fading observed in the substitution reaction between bromine and the saturated hydrocarbons. The usual test reagent is a 5 per cent solution of bromine in carbon tetrachloride, which is a common solvent for bromine and for all hydrocarbons. More or less hydrogen bromide is usually evolved when the bromine test is applied. This arises from an accompanying, slow, substitution reaction.

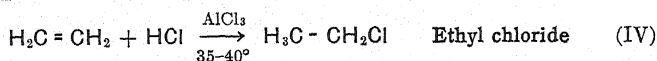
Addition of Acids. When an acid adds to an alkene, the attack on the unsaturation electrons of the double bond is led by a proton:



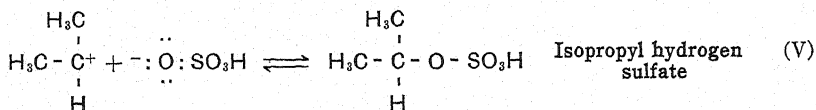
The resulting carbonium ion stabilizes itself immediately by adding a negative ion.

The *halogen acids* or hydrogen halides (HCl , HBr , HI) combine with alkenes to form alkyl halides, RX . Hydrogen iodide adds most readily and hydrogen chloride least, thus reversing the order of reactivity of the free halogens. The hydrogen halides may be used either as concentrated water solutions or as anhydrous gases. Metallic chlorides are

commonly used as catalysts with HCl gas in making alkyl chlorides. Thus very large amounts of ethyl chloride are manufactured by the reaction



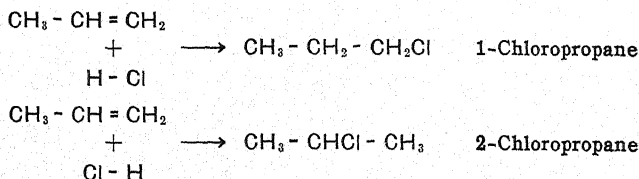
When an alkene is absorbed in cold *sulfuric acid*, the initial carbonium ion may react either with H_2SO_4 or with the bisulfate ion, HSO_4^- , to form an ester of sulfuric acid, *e.g.*,



The further reactions that may occur when an alkene is dissolved in sulfuric acid (polymerization, conversion to an alcohol, etc.) are discussed elsewhere.

Solubility Test for Alkenes. The ability of many alkenes to dissolve in cold sulfuric acid differentiates them from the acid-insoluble saturated hydrocarbons. The alkyl hydrogen sulfates are soluble in water, and no oily layer separates when their sulfuric acid solutions are diluted by pouring onto ice. This helps to distinguish alkenes from ethers and most other types of oxygen-containing organic compounds, which dissolve in cold H_2SO_4 but separate again on dilution. But the usefulness of these facts in practical tests is limited by the ease with which most alkenes polymerize (Sec. 3-12). The reaction between an alkene and H_2SO_4 is highly exothermic and, unless special precautions are taken to prevent any rise in temperature, much of the alkene is apt to be converted into polymers which are insoluble both in the acid and in water.

3-11 Direction of Addition. When *unlike* atoms or groups are added to an alkene, two isomeric products are usually possible.¹ This is because addition may occur in either of two directions, as illustrated by the following example:

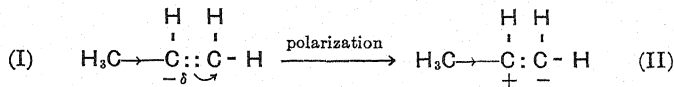


By the law of chance, both compounds should be formed in equal amounts. Actually, 2-chloropropane is the chief product of this reaction, with only a small amount of its isomer.

¹ The only exceptions are in additions to compounds which, like $\text{H}_2\text{C}::\text{CH}_2$ and $\text{H}_3\text{C}:\text{CH}::\text{CH}:\text{CH}_3$, are *symmetrical* with respect to the double bond.

Markownikoff's Rule. The observed facts in the above and many similar instances were summarized by Markownikoff¹ in a rule which has since been extended and is now usually stated as follows: In addition reactions at an ethylenic double bond, the more electronegative atom or group tends to unite with that carbon atom which carries the smaller number of hydrogen atoms. This rule has been found of great value in predicting the main products of many addition reactions.

Markownikoff also stated his rule in an equivalent form, to the effect that the more electronegative atom or group tends to unite with "that carbon atom which is more under the influence of other carbon atoms." This is of special interest in connection with the explanation now widely accepted. There is much evidence that a methyl or other alkyl group is somewhat more electron-releasing than a hydrogen atom.² Such an inductive effect of the CH₃ group in (I) would increase electron density on the secondary carbon atom. Hence, when (I) becomes polarized through any outside influence, it is likely to be in the direction of (II), the electrons of the double bond moving toward the primary carbon.



An attacking proton, or other positive ion, would therefore add to the primary carbon atom of the double bond, followed immediately by the addition of Cl^- or another negative ion to the secondary carbon. This is the direction of addition predicted by Markownikoff's rule.

The Peroxide Effect. For a long time the behavior of one particular substance—hydrogen bromide—in additions with alkenes appeared entirely unpredictable. In 1933, Kharasch discovered that the direction of addition of HBr depends upon the presence or absence of peroxides (or of oxygen). In the presence of a peroxide the reaction is more rapid, but the direction of addition is opposite to that predicted by the Markownikoff rule. By working in the total absence of oxygen and peroxides

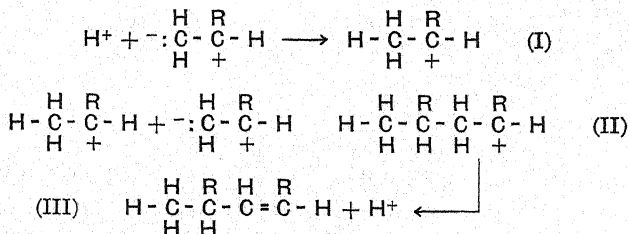
¹ Markownikoff's statement in *Liebig's Annalen*, **153**, 256 (1870), is as follows: "Wenn ein unsymmetrisch constituirter Kohlenwasserstoff sich mit einer Haloïd-wasserstoffsäure verbindet, so addirt sich das Haloid an das weniger hydrogenisirte Kohlenstoffatom, d. h. zu dem Kohlenstoff, welcher sich mehr unter dem Einflusse anderer Kohlenstoffe befindet."

² This property of a CH₃ group can be foreseen from the fact that hydrogen is slightly less electronegative (electron-attracting) than carbon, as shown by their respective values, 2.1 and 2.5, in the electronegativity scale (Sec. 1-9). This implies a slight displacement of electrons away from each of the three H atoms, the combined effect of which could be an appreciable increase in electron density on the CH₃ carbon atom.

(a condition best secured by having present a reducing agent or "inhibitor" such as hydroquinone), the "normal" or Markownikoff addition of hydrogen bromide can be effected, though somewhat slowly. The effect of the peroxide appears to be the formation of bromine *atoms*, which initiate the reaction by attacking the more electronegative carbon atom of the alkene.

3.12 Self-addition; Polymerization. Unsaturated hydrocarbons have a marked tendency toward a reaction which can be described as self-addition but which is usually called *addition polymerization*. A simple molecule which enters into such a reaction is known as the *monomer* (or monomeric form); the products formed by the addition of two, three, or four such molecules are called *dimers*, *trimers*, and *tetramers*, respectively. Some unsaturated compounds polymerize spontaneously or simply by heating or exposure to light; more commonly, catalysts are used. The most important polymerization catalysts are peroxides (Sec. 6.16), acids (H_2SO_4 , H_3PO_4), and certain halides such as AlCl_3 and BF_3 (Sec. 22.5).

The dimerization of an alkene with the aid of a catalyst such as H_2SO_4 probably proceeds as follows: A proton from the acid adds to the more electronegative carbon of a polarized monomer molecule, forming a carbonium ion (I); this attacks a second molecule of the monomer, forming the new carbonium ion (II); the latter stabilizes itself by expelling a proton, giving the dimer (III).

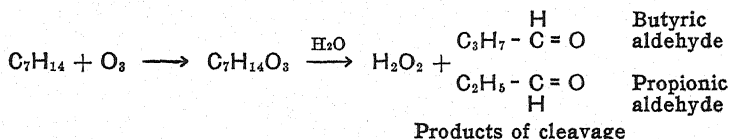


Alternatively (II) may add a third monomer molecule, leading to a trimer—and so on. *Polymerization* is a reaction which, in theory, is capable of proceeding indefinitely.

If the conditions are suitably chosen and carefully regulated, it is possible to obtain good yields of dimers from various alkenes. This is applied in one of the major methods for producing high-octane gasoline (Sec. 6.10). Under other conditions, unsaturated compounds yield *high polymers* in which hundreds of monomer molecules have united to form giant molecules of high molecular weight. This is considered in connection with its application to the manufacture of synthetic rubber and plastics (Secs. 6.15ff).

Polymerization often occurs when it is neither expected nor desired. It is usually responsible for the gummy or resinous nonvolatile substances which are obtained as by-products—sometimes as the major products—in various reactions in which unsaturated compounds are used or are formed.

3.13 Addition of Ozone; Ozonolysis. The higher alkenes readily add one molecule of ozone, O_3 , at the double bond, forming products called *ozonides*; ethylene and other simple alkenes react in like manner but less readily. Ozonides are often explosive and are seldom isolated. When treated with water they are decomposed, yielding hydrogen peroxide¹ and *two* partially oxidized organic molecules (aldehydes or ketones, Chap. 10). This method of splitting the alkene molecule is known as *ozonolysis*. Since cleavage always occurs at the double bond, the method may be used to “locate” the latter. Suppose, for example, it is applied to a compound of the composition C_7H_{14} , of unknown structure, with the results indicated below:



If the products can be identified as butyric aldehyde and propionic aldehyde, both of which are known to have normal chains with the oxygen atom at one end, the original alkene must have contained normal chains of four and three carbon atoms joined by a double bond. Hence its structure is (I) and that of its ozonide is (II):



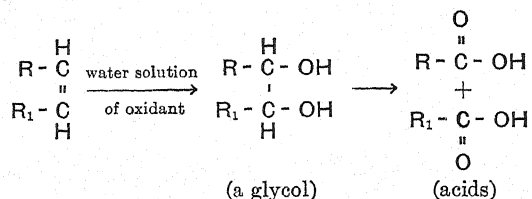
Any other position of the double bond or any chain branching would be reflected in different cleavage products.

It will be noted that the reaction with ozone differs from other alkene additions in that the reagent intrudes *between* the carbon atoms of the double bond.

3.14 Oxidation of Alkenes. Ozone is but one of many oxidizing agents which react with alkenes at the double bond. These include

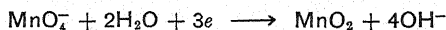
¹ Zinc dust and dilute acid are generally added in order to minimize the oxidizing action of H_2O_2 on the products of cleavage. Sometimes it is found preferable to split an ozonide by catalytic reduction with hydrogen and a nickel catalyst.

alkaline and acid solutions of potassium permanganate and dichromic acid, $\text{H}_2\text{Cr}_2\text{O}_7$. The first recognizable product with alkaline KMnO_4 at 0°C is a glycol, in which two hydroxyl groups have been added at the double bond:



Peroxides often give good yields of glycols (Sec. 16-4), but with most other oxidants these are further oxidized. Usually the molecule is split, at what was the alkene double bond, and each fragment oxidized to an acid.

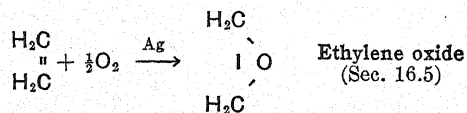
Permanganate Test for Unsaturation. Alkenes and other unsaturated hydrocarbons quickly reduce cold, dilute, slightly alkaline solutions of potassium permanganate. Evidence of reaction is the fading and disappearance of the purple color of the MnO_4^- ion and precipitation of brown hydrated manganese dioxide. Saturated hydrocarbons—if pure—do not respond. This useful distinguishing reaction is commonly called the *Baeyer test for the double bond*, although it is given also by acetylene and other hydrocarbons containing the *triple bond*. The reduction of permanganate ion in a dilute solution which is somewhat alkaline, or initially neutral, is expressed by the partial equation



Air Oxidation. Alkenes burn in air with flames that are more luminous than those of the corresponding alkanes. Flame luminosity is due to incandescent particles of carbon. The over-all equation for the complete combustion of ethylene is



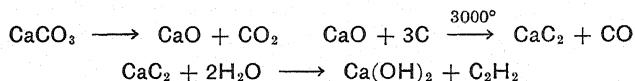
Specific intermediate oxidation products may be obtained by reaction with atmospheric oxygen at *regulated* temperatures and with suitable catalysts. For example, with silver as a catalyst at about 250°C , ethylene yields the important intermediate, ethylene oxide:



ALKYNES; ACETYLENE AND ITS HOMOLOGUES

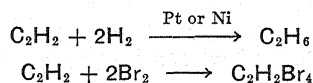
3-15 Acetylene, C_2H_2 , b.p. -84°C , is the simplest and by far the most important member of another series of unsaturated hydrocarbons

known as *alkynes*. Its chief present source in the United States (cf. Sec. 6.13) is the action of water on calcium carbide, obtained by heating limestone with coke in an electric furnace:

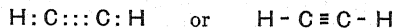


Acetylene can be produced cheaply where hydroelectric power is abundant, and this fact, coupled with high chemical reactivity, make it an important raw material for the manufacture of many organic compounds and their industrial products, *e.g.*, acetaldehyde, vinyl chloride, neoprene. Another extensive use is in the oxyacetylene blowtorch where, by burning with oxygen, flame temperatures of the order of 3000°C are produced and used for cutting and welding metals. Liquefied acetylene is explosive and dangerous to handle; the familiar steel cylinders in which it is shipped contain a solution in acetone, which dissolves 300 times its own volume of acetylene at a pressure of 12 atmospheres.

3.16 Triple Bonds. Acetylene resembles the alkenes in forming addition products with various substances. It differs in being able to add *four*—instead of only two—univalent atoms to its molecule, *e.g.*,



This higher degree of unsaturation is ascribed to a *triple* bond between the carbon atoms, formed by the sharing of *three* pairs of electrons. The triple bond is represented in formulas in either of the following ways:



A conventional model for acetylene is pictured in Fig. 3.2.

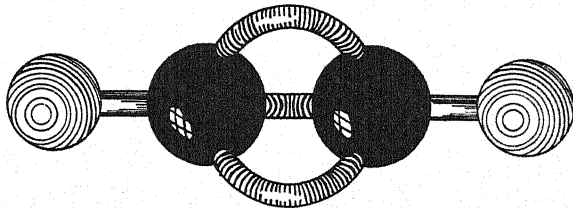


FIG. 3.2 Model representing the molecule of acetylene, C_2H_2 .

Physical evidence for the triple bond is found in the shortened distance between the carbon atoms in acetylene (1.20 \AA) as compared with the $\text{C}=\text{C}$ bond in ethylene (1.34 \AA) and the $\text{C}-\text{C}$ bond in ethane (1.54 \AA). The heat of formation of acetylene shows that energy must be expended

to bring carbon atoms as close together as they are when joined by a triple bond.

Heats of Formation. The amount of heat evolved or absorbed in producing one mole of a compound from its elements is called its heat of formation. Usually this cannot be measured directly. It may be calculated, however, by comparing the heat of combustion of one mole of a compound with that of the same weights of its elements in the free state. The equation for the complete combustion of one mole (26 grams) of acetylene is

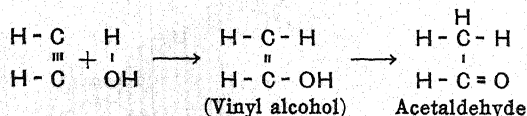


Since the heat evolved in the complete combustion of 24 grams of pure carbon and 2 grams of hydrogen is only 256.4 kcal, the heat of formation of C_2H_2 is +54.2 kcal. In other words, acetylene is an *endothermic* compound, containing more energy than its elements. This additional energy is partly responsible for the high temperatures obtainable in the oxyacetylene flame. And we may think of it also as contributing to the high chemical reactivity of the substance.

In contrast with acetylene, the heat of combustion of 1 mole (30 grams) of ethane is 20.2 kcal less than that of 24 grams of carbon and 6 grams of hydrogen. This negative heat of formation shows that ethane is an *exothermic* compound, containing less energy than its elements. The same holds true for all saturated hydrocarbons. Ethylene occupies a position intermediate between ethane and acetylene; it is *endothermic*, like acetylene, but the heat of formation is only +12.5 kcal.

3.17 Acetylene Reactions. Acetylene is oxidized by many reagents including permanganate solutions, it polymerizes (Sec. 6.16), forms many addition products, and yields metallic derivatives. A few specific reactions are described below and others in later chapters.

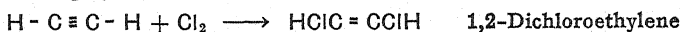
Hydration to acetaldehyde by the catalytic addition of water is a major reaction of acetylene in chemical industry. This is accomplished by passing the gas through a hot, dilute solution of sulfuric acid containing mercuric sulfate as a catalyst. The reaction involving the catalyst is complex, but its net result is the addition of a molecule of water to form vinyl¹ alcohol; the latter cannot be isolated because it tautomerizes immediately (Sec. 20.13) to acetaldehyde:



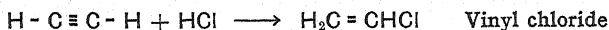
Regulated Additions. While the triple bond is readily able to add two molecules of hydrogen, halogens, hydrogen halides, etc., it is possible to find conditions under which only one molecule is added. This is often advantageous because the products of such regulated additions are still unsaturated and therefore more reactive and more useful. As an example, when acetylene in large *excess* is mixed with chlorine, addition can be

¹The unsaturated group, $\text{H}_2\text{C}=\overset{\text{H}}{\text{C}}\cdot$, is called the *vinyl* radical. This term is frequently used in naming compounds containing it.

restricted largely to the reaction



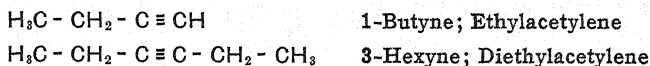
More important is the controlled, catalytic addition of hydrogen chloride:



Acetylides. Acetylene differs from both the alkanes and alkenes in that its hydrogen atoms are replaceable by certain *metals*. These metallic derivatives are called *acetylides*. Calcium carbide may be considered an example; another is sodium acetylide, Na_2C_2 , which can be made by passing acetylene over warm metallic sodium. Cuprous and silver acetylides are explosive when dry.

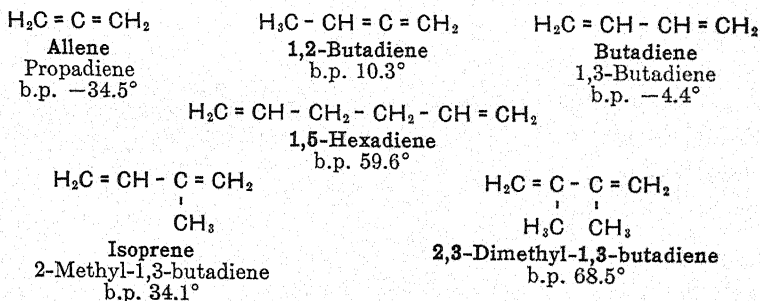
Test for the Triple Bond. When acetylene is passed into an ammoniacal solution of a cuprous salt, red-brown cuprous acetylide, $\text{Cu} \cdot \text{C} \equiv \text{C} \cdot \text{Cu}$, is promptly precipitated. This test is useful for distinguishing acetylene and some of its homologues from hydrocarbons of all other types. It is limited, however, to compounds of the type $\text{R} : \text{C} :: \text{C} : \text{H}$, in which there is a hydrogen atom on one of the triply bound carbon atoms.

3-18 Acetylene Homologues. Other aliphatic hydrocarbons containing a triple bond form with acetylene the homologous series of alkynes, of the general formula $\text{C}_n\text{H}_{2n-2}$. The known homologues of acetylene are neither numerous nor of much present importance. Systematically, they are named from the corresponding alkanes by changing the terminal *-ane* to *-yne* (in the original Geneva system, as used in Beilstein, the termination is *-ine*). More commonly, they are named as derivatives of acetylene in which one or both hydrogen atoms have been replaced by as many alkyl radicals. Both systems are illustrated by the following examples:



ALKADIENES; CONJUGATION

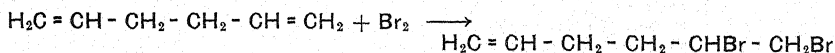
3-19 Aliphatic hydrocarbons containing two double bonds are called *alkadienes* or *diolefins*. Their general formula, $\text{C}_n\text{H}_{2n-2}$, is the same as that for the alkynes, and corresponding members of the two series are isomeric. The systematic names of individual compounds are formed from those of the corresponding alkanes by replacing the terminal *-ne* by *-diene*. Positions of the double bonds are indicated by numbering in the usual way, as illustrated:



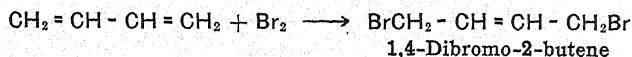
These examples also illustrate an important difference in the *relative positions* of the double bonds. If both involve the same carbon atom (as in propadiene and 1,2-butadiene), the system is called *cumulated*; only a few compounds of this type are known, and they are of no present importance. If there are one or more carbon atoms between those carrying the double bonds (as in 1,5-hexadiene), the system is called *separated* and the double bonds are described as isolated. If two carbon atoms carrying double bonds are attached to each other (as in 1,3-butadiene and in isoprene), the system is *conjugated*. Such conjugated systems are of special interest and importance.

General Chemical Properties. As would be expected, the alkadienes behave as typical unsaturated compounds. They are easily oxidized by various chemical reagents,¹ including alkaline permanganate solutions. They add hydrogen, halogens, and hydrogen halides under conditions similar to those for the alkenes but in all such reactions are capable of adding *two* molecules (four univalent atoms). The conjugated alkadienes polymerize with exceptional ease, and this is their most important property; natural rubber is a polymer of *isoprene*, and the largest process for making synthetic rubber is based on the polymerization of 1,3-butadiene.

3.20 Conjugation and Addition. Conjugated alkadienes differ from the other types in addition reactions which are so controlled that only *one* foreign molecule (*e.g.*, of H_2 or Br_2) is added. When one molecule of bromine adds to a compound like 1,5-hexadiene in which the double bonds are *separated*, the halogen adds to both carbon atoms of one bond as would be expected, leaving the other unaffected, *e.g.*,



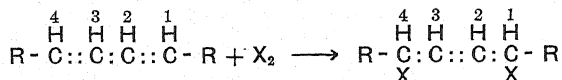
This is *not* the usual result if the double bonds are conjugated. For example when one molecule of bromine adds to 1,3-butadiene, the principal reaction product is a compound in which the bromine atoms have added *at the ends* of the conjugated system:



The 1,2-dibromide is also formed but to a smaller extent.

Generalizing, it is observed that when two double bonds are conjugated the prevailing mode of addition is to C^1 and C^4 of the conjugated system with a new double bond appearing between C^2 and C^3 :

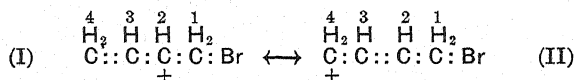
¹ Some conjugated alkadienes, such as 1,3-butadiene, rather easily take up atmospheric oxygen to form unstable, explosive peroxides. This must be guarded against when working with them. Peroxide formation can be avoided by the presence of suitable reducing agents or *inhibitors*.



This mode of reaction is described accordingly as 1,4-addition. It is important in the polymerization of compounds such as isoprene and butadiene and is utilized in the general method of synthesis known as the Diels-Alder reaction.

Longer conjugated systems are also known (see Sec. 4-13 for examples), and these likewise tend to addition at the *ends* of the system, even when they are far removed from each other. This behavior is only one of several facts which show that, when conjugated, double bonds tend to lose their individual identity and to *act as a unified system*.

3-21 The 1,4-additions of conjugated systems are explained as follows. Assuming the addition of Br^+ to butadiene, as in Section 3-8, the resulting carbonium ion would be represented by (I). Obviously the unit plus charge on C^2 would exert a strong pull on the unsaturation electrons of the double bond and thus tend to form (II), with the plus charge on C^4 .



According to the theory of *resonance* (Chap. 5) the carbonium ion does not have either of these structures but is a hybrid—something in between, which partakes of the nature of both. An outside force can readily *polarize* it in either direction. Hence, in adding a Br^- ion it may act either as (I), giving 1,2-addition, or as (II), giving 1,4-addition.

TESTS FOR DISTINGUISHING BETWEEN HYDROCARBONS

3-22 Pure specimens of saturated and unsaturated aliphatic hydrocarbons are readily distinguished from each other by simple laboratory tests based on the differences in properties already described. The most useful tests for *unsaturated* hydrocarbons are the prompt reduction of a cold, dilute solution of potassium permanganate and the rapid decolorization of bromine. If both of these are negative, the absence of a double or a triple bond is established, and the substance must be *saturated*. The test with ammoniacal cuprous chloride distinguishes between certain alkynes and other types of unsaturated hydrocarbons. *Pure* specimens of saturated hydrocarbons do not affect permanganate and react with bromine very slowly and with the evolution of hydrogen bromide. They do not dissolve in cold concentrated sulfuric acid and are unaffected by it. The *cold* acid dissolves some alkenes, but may cause polymerization; more highly unsaturated hydrocarbons are usually polymerized quickly by contact with sulfuric acid, often with the formation of dark resinous products.

In testing commercial products such as gasoline and kerosene, discretion is needed in interpreting the results. Such products are always *mixtures* and usually contain enough alkenes to give strong tests for unsaturation even if they are composed mainly of alkanes.

3-23 Study Aid. One of the most valuable aids in the study of organic chemistry is the practice of seeking correct answers to such questions as: *How would you distinguish by chemical tests between n-octane and 2-pentene?* The information needed to answer this particular question has just been summarized, but the general principles deserve further attention and emphasis.

When asked this question, or one of like nature, the student should picture himself in the laboratory confronted by two unlabeled specimen tubes. In the present instance, let him assume that each of these contains about 5 ml of colorless liquid which he is justified in assuming to be a pure compound. Just how should he proceed?

Obviously, he must know the chemical properties of the two substances in question—or those of the *classes* of compounds to which they belong. Furthermore, he must be able to *compare* these properties and eliminate those which are common to both; tests must utilize the significant *differences*. Considering the matter from the practical laboratory standpoint, he will realize that each test should meet the following requirements: (1) It should require only a small amount of material and very simple apparatus, preferably only a test tube. (2) It should require but a few minutes to perform and reach a conclusion. (3) It should give a readily recognizable change—such as the evolution of a gas, a substance passing into or out of solution, a change in color, or the development of a characteristic odor—with *one* of the substances, while the other is either unaffected or acts in an entirely different manner. (4) It should be based, preferably, upon reactions and properties that the student has observed in his own laboratory work. Careful consideration of these requirements will show that many reactions employed in the time-consuming laboratory “preparations” are not well suited for use in distinguishing between substances.

Tests that give distinct changes—such as those observed when an alkene is treated with permanganate—are described as *positive*. Because of their chemical inertness alkanes seldom give any positive test and must be recognized by *failure* to respond to the tests for unsaturation. Plainly, positive results are more desirable. In general, when asked how he would distinguish between compounds *A* and *B*, the student should be prepared to give at least one practical positive test for *A* and likewise a practical positive test for *B*. When this is done, the differentiation may be regarded as conclusive.

Questions

1. Summarize the essential differences between carbon-to-carbon single and double bonds.

2. (a) Write the structural formulas of all the possible pentenes and give their systematic names. (b) Compare with the number of pentanes and explain the difference.

3. Write structural equations and specify essential reagents and conditions for the over-all reactions involved in the manufacture or preparation of propene from: (a) propane; (b) *n*-propyl alcohol, $\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$; (c) 1,2-dichloropropane; (d) 2-bromopropane.

4. Write structural over-all equations for the formation of alkenes when the following are heated together; if two organic products may be formed, show the origin of each: (a) 1,2-dibromohexane and sodium; (b) 2-bromopropane and alcoholic KOH;

(c) 2-bromopentane and alcoholic KOH; (d) *n*-hexyl alcohol (1-hydroxyhexane) and a dehydrating acid; (e) 2-hydroxyhexane and a dehydrating agent.

5. (a) Distinguish between molecular polarization and polarizability. (b) Show how cleavage of the covalent bond C:Y in different ways might lead to the formation of a carbonium ion, a carbanion, or a free radical. (c) Distinguish between the terms electrophilic and nucleophilic.

6. Explain in detail the direction and the *course* of the addition reaction between HCl and isobutylene.

7. With the aid of Markownikoff's rule when necessary, write the structural formula for the principal product to be expected in the reactions between: (a) 2-methyl-2-butene and HBr (peroxide-free conditions); (b) 1-pentene and cold H_2SO_4 ; (c) 2-pentene and cold, dilute KMnO_4 solution (initial product only); (d) 3-hexene and HCl

8. (a) Define polymerization. (b) Show that a dimer of $\text{RHC}=\text{CH}_2$ might have a structure different from that shown in Section 3-12. (c) Write structural equations showing in detail how 1-butene might be expected to dimerize and trimerize under the influence of an acid catalyst.

9. A student was attempting to prepare 2-pentene (b.p. 36.4°C) from secondary amyl alcohol, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$, by the use of sulfuric acid as a dehydrating agent. The bulk of his product was a liquid that distilled between 140 and 160°C . Account for the formation of this high-boiling product.

10. An alkene of the composition C_6H_{12} was treated with ozone and the resulting ozonide decomposed by water. The products isolated were shown to have the structures indicated by the formulas $\text{CH}_3\text{CH}_2\text{CHO}$ and CH_3COCH_3 . Write the structural formula of the original alkene and the equation for its reaction with ozone.

11. Applying the principles illustrated in Section 3-6, write structural equations for the formation of acetylene from $\text{C}_2\text{H}_2\text{Cl}_4$ and $\text{C}_2\text{H}_4\text{Cl}_2$, specifying reagents and conditions.

12. Ethylene dichloride (1,2-dichloroethane) is formed by the action of chlorine on either ethane or ethylene. Explain why the latter method is generally used in practice, even when the ethylene required has to be made from ethane.

13. Write structural equations for several reactions illustrating the addition reactions of acetylene: (a) when unrestricted; (b) under controlled conditions.

14. (a) Show that an alkadiene is isomeric with any corresponding alkyne. (b) Write the structural formula of a compound containing a conjugated system of three double bonds. (c) If the last compound reacted with one (only) molecule of bromine, show what isomeric products might be expected.

15. Assuming that 1,3-butadiene polymerizes by 1,4-addition and that the dimer has a normal chain, write the structural equation for its dimerization.

16. Write a possible structural formula for a compound of the composition shown in the first column which could react in such a way as to yield the product given in the last column:

Original substance	Reagent	Product
(a) C_4H_8	HBr	$\text{C}_4\text{H}_9\text{Br}$
(b) C_4H_{10}	Br_2	$\text{C}_4\text{H}_9\text{Br}$
(c) C_6H_{12}	KMnO_4	$\text{C}_6\text{H}_{14}\text{O}_2$
(d) C_6H_{12}	Cl_2	$\text{C}_6\text{H}_{10}\text{Cl}_2$
(e) C_3H_6	H_2SO_4	$\text{C}_3\text{H}_8\text{SO}_4$
(f) C_4H_6	HI	$\text{C}_4\text{H}_8\text{I}_2$

17. Using bromine water (or bromine in carbon tetrachloride), a dilute solution of potassium permanganate, concentrated sulfuric acid, and an ammoniacal solution of cuprous chloride as reagents, give as many ways as possible to distinguish between the following compounds (if distinction is possible) and describe accurately the *observations* on which you would base your conclusions: (a) *n*-hexane and 2-hexene; (b) 2-hexene and 1-hexyne; (c) 1-hexyne and 2-hexyne; (d) 2-hexyne and 2-hexene; (e) 1,5-hexadiene and 1-hexyne.

CHAPTER 4

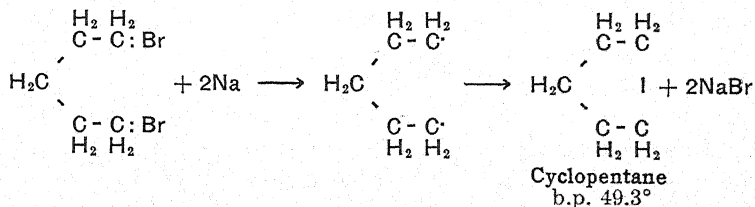
CARBON RINGS

ALICYCLIC AND RELATED HYDROCARBONS

Crude petroleum from many fields contains hydrocarbons that do not belong to any of the homologous series yet described. Two of the commonest have the molecular formulas C_5H_{10} and C_6H_{12} and are therefore isomers of the pentenes and hexenes, respectively. But in their chemical properties they show little resemblance to these or to any other unsaturated hydrocarbons. They do not react by addition with hydrogen or the free halogens or the hydrogen halides; they do not polymerize; they are unaffected by permanganate and by most other oxidizing agents. In brief, they closely resemble such *paraffin* hydrocarbons as pentane and hexane and must be regarded as fully saturated.

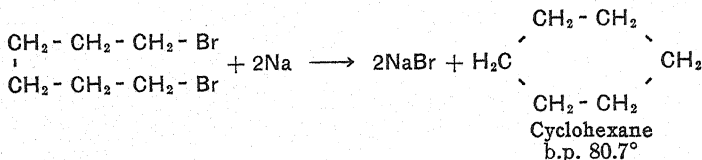
The question that arises is: How can these compounds be saturated when their molecules contain two atoms of hydrogen less than the corresponding alkanes?

4.1 Ring Formation. This question has been answered by synthesis. When 1,5-dibromopentane is heated with sodium, NaBr is formed as in the ordinary Wurtz-Fittig reaction. The major organic product is a hydrocarbon of the composition C_5H_{10} , which is identical in boiling point ($49.3^\circ C$) and all other properties with the compound of this formula isolated from petroleum. It may be assumed that, when sodium removes two bromine atoms, C^1 and C^5 are each left with an unpaired electron (Sec. 2.6) and that these atoms then unite through electron pairing to form a saturated *closed chain* or *carbon ring*:

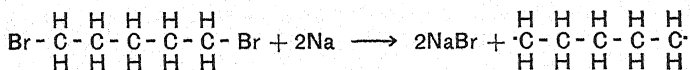


Emphasizing this structure and the chemical resemblance to *n*-pentane, the resulting hydrocarbon is known as *cyclopentane*.

In like manner *cyclohexane*, containing a saturated six-carbon ring, is formed by the action of sodium on 1,6-dibromohexane:



4.2 Space Relations. When sodium removes bromine from a compound such as 1,5-dibromopentane, it is easy to predict the possible formation of an unsaturated radical with an unpaired electron at each end of a five-carbon chain:



But when the formulas are written in the usual way, as above, it is not so easy to see why and how the ends of such a chain *approach each other*, as is necessary in order to join and form a ring.

By using the conventional models, which indicate positions in space, this becomes readily understandable. Such models (Figs. 4.1 and 4.2)

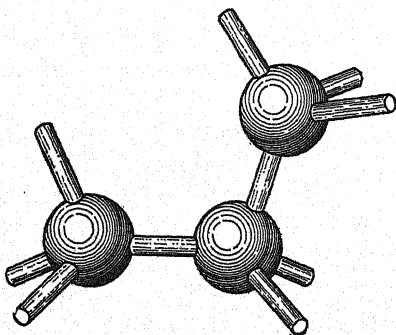
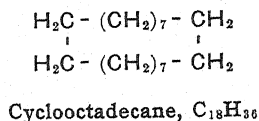
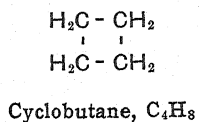
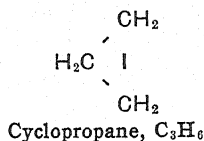


FIG 4-1 Model showing that three carbon atoms cannot lie in a line.

make it clear that three or more atoms in a carbon chain can *never* lie in the straight line suggested by ordinary written formulas. The models also suggest that any two atoms joined by a single bond should be able to rotate easily, like wheels on an axle, about the line between their centers. There is much direct evidence that such a rotation about single bonds requires little expenditure of energy and actually occurs in nearly all instances. Thus it becomes apparent how a five-carbon chain can assume innumerable positions, so that C¹ and C⁵ may be at one time quite remote from each other and, again, very close together (Fig. 4.2). The action of sodium or zinc on 1,5-dibromopentane leaves C¹ and C⁵ each with an odd electron; these can pair, from the position indicated in Figure 4.2b, to form a new covalent bond which closes the ring.

4.3 Cyclanes. The saturated hydrocarbons analogous to cyclopentane and cyclohexane, which contain *one* ring, form a homologous series of the general formula C_nH_{2n}. They are called *cyclanes* or *cycloparaffins* and—in the petroleum industry—*naphthenes*. Hydrocarbons of this series are known in which the rings contain 3 to 34 carbon atoms.

Individuals are named from the corresponding alkanes by prefixing *cyclo*, e.g.,



The cyclanes are widely distributed in nature and are important components of petroleum. The most abundant are those containing rings

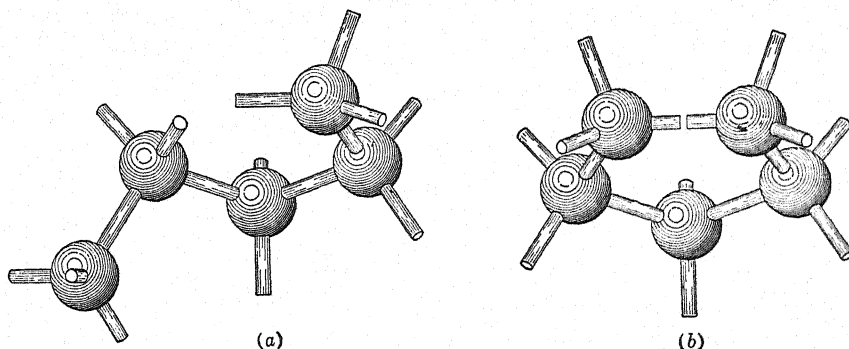
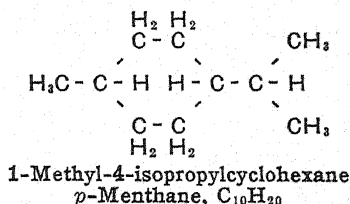
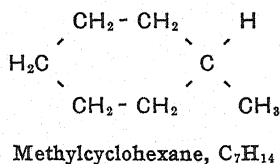


FIG. 4-2 Models showing how the terminal atoms in a five-carbon chain may be at one instant far apart (a) and, at another, close together (b).

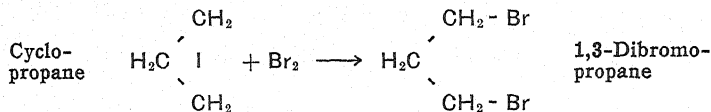
of five or six carbon atoms with one or more alkyl *side chains* attached, e.g.,



Properties. Cyclopentane, cyclohexane, and other cyclanes containing rings of *five or more* carbon atoms so closely resemble the alkanes in chemical properties that it is impossible to distinguish one from the other by ordinary qualitative tests. The rings are extremely stable; they are not opened by vigorous reduction methods such as catalytic hydrogenation, nor by oxidizing agents except under very severe conditions. Bromine and chlorine react but only by substitution.

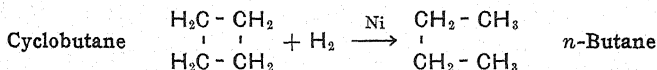
4.4 Small Rings. Rings of *three* carbon atoms and—to some extent those of *four*—lack the high stability and low reactivity just described.

Cyclopropane reacts *by addition* with bromine, hydrogen bromide, sulfuric acid, and hydrogen (by nickel catalysis). Each of these reactions involves opening the ring by cleavage of a carbon-to-carbon bond, *e.g.*,



Thus the behavior of cyclopropane with these reagents is similar to that of the alkenes (though it differs in not being affected by permanganate and in not adding ozone). The effectiveness of cyclopropane as a general anesthetic is probably connected with its chemical reactivity.

The four-carbon ring is considerably more stable. Cyclobutane does not react in the cold with the reagents just mentioned but, at higher temperatures, bromine and hydrogen bromide open the ring and form addition products; hydrogen is added by nickel catalysis but only at temperatures higher than required for cyclopropane:



Molecular heats of combustion also show significant differences. For cyclopentane, cyclohexane, and cyclanes with larger rings, the values are about the same per CH_2 as in the alkanes—that is, about 156 to 158 kcal per mole. For cyclobutane the corresponding value is 165.5, and for cyclopropane it is 168.5 kcal. In other words, these small-ring molecules actually possess the greater total energy which their reactivity suggests.

4.5 Strain Theory; Tetrahedral Carbon Atom. The lower stability of three- and four-carbon rings as compared with larger ones was explained by Adolph von Baeyer (1885) in terms of what is called the *strain* theory. From the facts of stereoisomerism (Chap. 17) J. H. van't Hoff had reached the conclusion (1874) that the four valences of a carbon atom must make equal angles in space. This common angle he calculated to be $109^\circ 28'$, which is the angle between any two of the four lines from the center of a regular tetrahedron to its vertices. Thus arose the concept of the *tetrahedral carbon atom*, a term which conveys the idea that any carbon atom is to be regarded as situated at the center of a regular tetrahedron with four attached atoms or groups at its vertices. Figure 4.3 shows that our ordinary mechanical models are based on this conception. We have noted already (Sec. 1.11) that the tetrahedral angle of $109^\circ 28'$ which van't Hoff calculated by a process of pure reasoning has been observed (to a close approximation) in many carbon compounds by the use of X-ray spectroscopy and other physical methods which only became available many years after his death.

Starting with this concept of the tetrahedral angle, Baeyer reasoned as follows. If the carbon atoms in cyclopropane are equidistant from each other, lines joining their centers must form an equilateral triangle and make angles of 60° with each other. Hence, if the valence forces

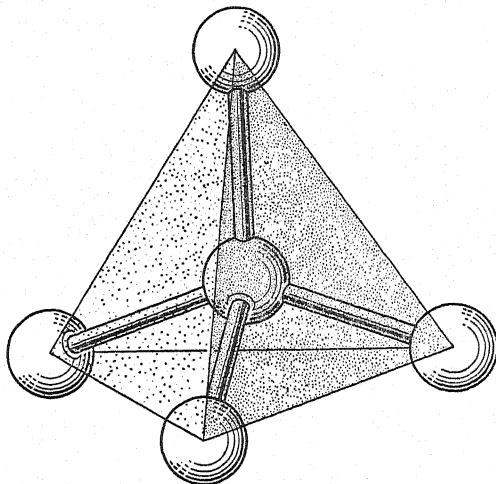


FIG. 4-3 The tetrahedral carbon atom.

(bonds) between carbon atoms act in straight lines, they must be *bent toward each other*. Baeyer regarded such a deflection of the valences from their normal directions as causing a tension or *strain* which is responsible for the marked tendency of three-carbon rings to open up and form addition products.

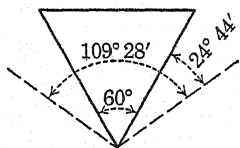


FIG. 4-4 Calculation of strain in a three-carbon ring.

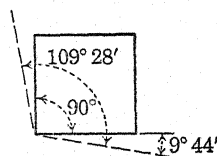


FIG. 4-5 Calculation of strain in a four-carbon ring.

According to this hypothesis, the intensity of the strain in any ring is measured by the angle through which each valence is bent. In cyclopropane, the angle of deflection would be one-half the difference between $109^\circ 28'$ and 60° , or approximately 25° (Fig. 4-4). A similar calculation for cyclobutane (Fig. 4-5) gives an angle of deflection of $9^\circ 44'$, and for cyclopentane this becomes *less than* 1° . Hence, Baeyer argued, a five-carbon ring is under substantially no strain and its observed stability is explained.

The principle of Baeyer's argument can be shown also by working with molecular models. If there are five "carbon" balls in a chain, such a model offers no resistance when one attempts to join the ends by a pin (compare Fig. 4-2b). But with a three-ball model (Fig. 4-1) it is impossible to close the ring if the connecting rods are rigid; if they are somewhat elastic, considerable pressure must be exerted and the resulting ring system is under obvious mechanical strain and tends to fly open. With a four-ball model there is appreciable strain, but much less than with only three.

In more recent times the "strain" which obviously exists in small rings is explained in terms of electron repulsions, as follows. The four pairs of bonding electrons which unite a carbon atom with any four other atoms mutually repel each other and therefore seek (average) positions as far apart as possible. This favored situation exists when lines joining the four other atoms to carbon make the tetrahedral angle of $109^{\circ}28'$. Reducing this angle means that the electron pairs are brought closer together and therefore exert stronger repulsions.

4-6 Strainless Large Rings. Cyclohexane and cyclanes containing larger rings give no evidence of strain. Molecular models show that this is to be expected, if we do not assume that all the carbon atoms must lie in a plane. Such a model for cyclohexane shows that a slight but

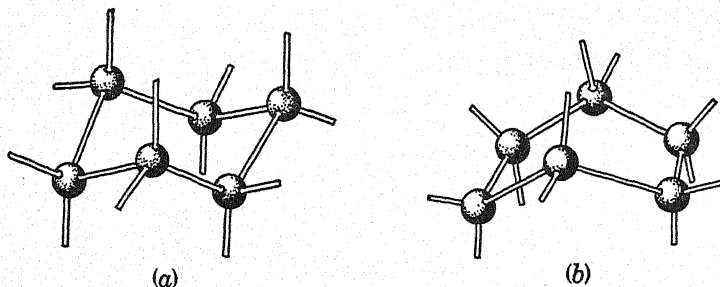
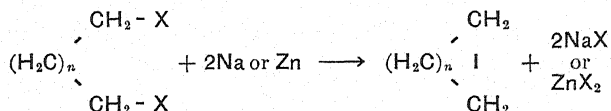


Fig. 4-6 Strainless models of cyclohexane, C_6H_{12} . These represent the *same* substance and not two isomers because—as the wooden models show—neither form is rigid and each shifts readily into the other.

recognizable pressure is necessary to force the six carbon balls into a plane. When this is done, the arrangement is found to be unstable; if the pressure is relaxed and the model given a slight jar, it slips easily into one or the other of the strainless arrangements pictured in Figure 4-6. Each of these also slips easily into the other, thus explaining why only one form of cyclohexane is known. Combined physical and chemical evidence supports the view that all rings of six or more carbon atoms are strainless because they have some such *crumpled* or *puckered* structures.

At the time Baeyer advanced his strain theory, there were known only a few compounds containing rings of more than six atoms. Baeyer argued that this was due to an *outward strain* (bond angles greater than $109^{\circ}28'$) which must exist and may be calculated if all the carbon atoms *lie in plane*, as he assumed. As soon as we admit that the latter assumption is unnecessary, and that the rings may be crumpled, the argument for a strain disappears and the stability of large rings is explained.

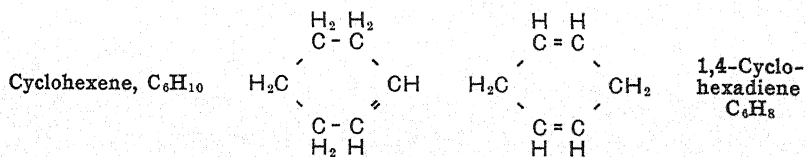
4.7 Methods of Ring Closure. The method described for the formation of cyclopentane, known as the Freund reaction, is summarized by the type equation



It can be applied also to branched-chain compounds such as 3-methyl-1,5-dibromopentane. A modification of it is used in producing cyclopropane (for use as a general anesthetic), and it gives fair yields of compounds containing four-, five-, and six-membered rings but is practically useless for forming larger rings. This limitation is probably due to the fact that, as the length of an open-chain molecule increases, the position favorable for ring closure shown in Figure 4.2b arises less frequently.

Other general methods for forming carbon rings include the Diels-Alder synthesis (Sec. 19.6) and one based on heating the salts of certain acids (Sec. 19.8). It should be mentioned also that the hydrogenation of aromatic compounds (Chap. 5) is an important source of *six-carbon* saturated rings. This does not involve ring closure but utilizes the preformed rings of benzene and related compounds.

4.8 Unsaturated Cyclic Hydrocarbons. In the cyclanes just described, all carbon atoms are joined by *single* bonds. There are known, also, some unsaturated cyclic hydrocarbons. Those in which two carbon atoms of the ring are joined by a double bond are called *cyclenes* (general formula $\text{C}_n\text{H}_{2n-2}$); those containing two such double bonds (general formula $\text{C}_n\text{H}_{2n-4}$) are *cyclodienes*; *e.g.*,



These compounds behave entirely like the alkenes and alkadienes of the open-chain series. Under similar conditions they add hydrogen, halogen acids, etc. They quickly reduce permanganate; the latter, and other

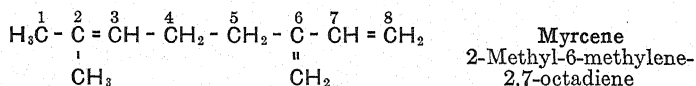
oxidizing agents, readily split the carbon ring at a double bond and yield open-chain products. Polymerization is another general property. In short it appears that a double bond between two carbon atoms of a *ring* has properties no different from those observed in ethylene and other open-chain hydrocarbons.

TERPENES AND RELATED HYDROCARBONS

4.9 Terpenes are unsaturated hydrocarbons of the formula $(C_5H_8)_n$. Those which are most common have the composition $C_{10}H_{16}$ (*i.e.*, $n = 2$). Many terpenes and their derivatives are widely distributed in plants, particularly those of the coniferous and citrus families.

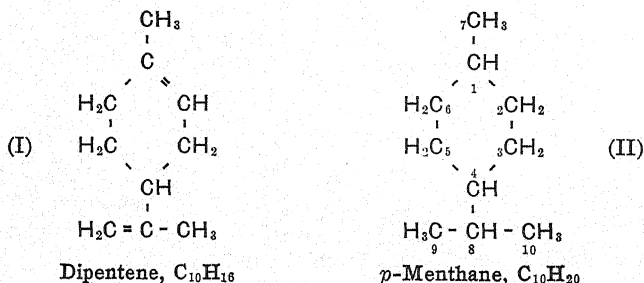
Classification. Terpenes of the formula $C_{10}H_{16}$ contain six fewer hydrogen atoms than the corresponding alkanes (the decanes, $C_{10}H_{22}$). This shortage of hydrogen is accounted for in the three classes of simple terpenes as follows:

1. *Olefinic* terpenes are open-chain hydrocarbons containing three double bonds, *e.g.*,



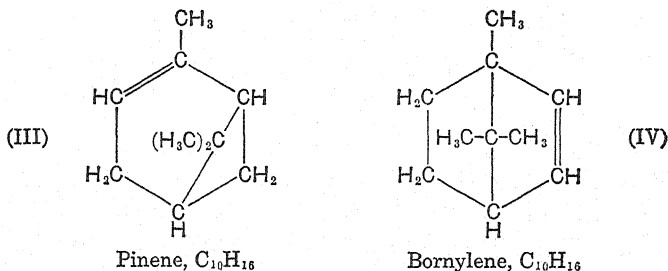
Only a few are known, and these are not abundant. However, alcohols and other oxidation products related to them are plant products of some industrial importance.

2. *Monocyclic* terpenes contain two double bonds and one closed ring, as in dipentene (I). Most of these contain the carbon framework of *p*-menthane (II), in which a methyl group and an isopropyl group are attached to a six-carbon ring in the 1,4 positions. Dipentene is one of the 14 isomers which are made possible by different positions of the two double bonds.



3. *Bicyclic* terpenes contain *one* double bond and *two* closed rings. One of the rings is always six membered; the other is described as forming a

bridge in one or the other of the positions illustrated by the formulas for pinene (III) and bornylene (IV):



The actual structure can be visualized better by thinking of the quaternary carbon atom, shown inside the six-membered ring, as lying above the plane of the paper (Fig. 4-7).

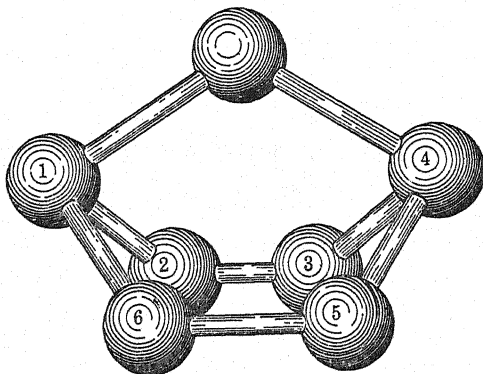


FIG. 4-7 Model of a six-carbon ring with a carbon "bridge" between C^1 and C^4 .

Since all terpenes contain at least one double bond, they form various addition products, as would be expected. They polymerize when strongly heated and by contact with concentrated sulfuric acid. They are readily oxidized and are often accompanied in nature by oxygen derivatives, mainly alcohols, aldehydes, and ketones. Any detailed study of terpene chemistry is much too complicated for a beginning text. Some industrial sources and relations are considered below.

4-10 Turpentine and Rosin. Crude turpentine is a sticky viscous balsam or oleoresin secreted by many varieties of coniferous trees. Its chief source is the pine tree, from which the exudate is collected in a cup set below a V-shaped gash in the trunk. When distilled with steam,

this crude product is separated into a distillate known as *turpentine oil*, or *spirits of turpentine*, and a residue of *rosin*. Similar products are also obtained from pine stumps by chipping to about the size of match sticks, charging into stills, and passing in live steam. This carries over the turpentine oil and the somewhat higher boiling *pine oil*. The chips are then extracted with hot petroleum naphtha or a similar solvent to dissolve out the remaining pine oil and the rosin.

Refined turpentine (b.p. 154 to 159°C) is a mixture of terpenes in which *pinene* greatly predominates. It is an excellent solvent for fats, oils, and waxes and is used in large quantities as a thinner in paints and varnishes. More recently, it has been utilized as a source of pure individual organic compounds; for example, large amounts of synthetic camphor (Sec. 10-16) are now manufactured from pinene obtained from turpentine.

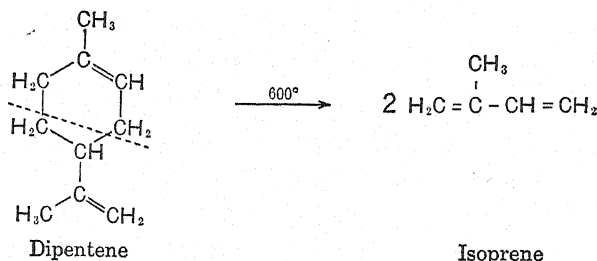
Rosin. The product commonly called rosin is typical of the *resins* that are nearly always associated with terpenes in nature. These are amorphous solids of high complexity which appear to have been formed from terpenes by polymerization and oxidation. Ordinary rosin consists largely of resin acids, $C_{20}H_{30}O_2$ (Sec. 11-11). It is used extensively as a paper size, in making laundry soaps, and in "modifying" alkyd resins (Sec. 24-14).

The production and distribution of turpentine and rosin is commonly called the *naval-stores* industry, a term which originated in the days of wooden sailing vessels.

4-11 Essential Oils. The odors of most plants are due to water-insoluble oily substances contained (usually in small amounts) in their fruits, flowers, leaves, or stems. Unlike the fatty oils (Chap. 16), these can be distilled, either alone or with steam, and for this reason they are sometimes called *volatile oils*. More commonly, they are known as *essential oils*. (This term is derived from the word *essence* and does not mean *necessary*.)

Most of the essential oils are mixtures of terpenes and terpene oxidation products (cf. Sec. 15-18). These include the oils of citronella, lemon, peppermint, rose, spearmint, and many others. They are usually separated from plant tissues by steam distillation or, less commonly, by pressure (e.g., oil of lemon from lemon peel), or by extraction with suitable solvents. A major use is in the manufacture of perfumes and flavors.

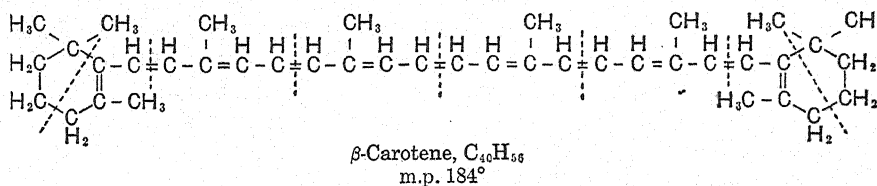
4-12 Relations to Isoprene. The simplest compound having the terpene formula is isoprene, C_5H_8 , which is sometimes described as a *hemiterpene*. There is an interesting relationship between isoprene and the true terpenes. Several of these yield isoprene when strongly heated; e.g., dipentene splits along the line indicated to give two molecules of isoprene:



Conversely, isoprene can be dimerized under some conditions to yield terpenes. Any terpene formula can be constructed by combining isoprene units (sometimes with other minor changes which appear reasonable), but there is no direct evidence that they are built up this way in nature. They are generally believed to be waste products from some step in plant life.

The isoprene unit appears also in a number of other important types of compounds found in plants. We shall describe here the polyene pigments and natural rubber.

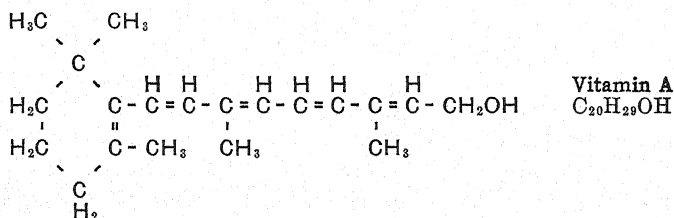
4.13 Polyene Pigments; Vitamin A. Compounds containing a number of double bonds are called polyenes. Those polyenes which contain as many as five double bonds in conjugation are colored (Chap. 25), the hue ranging from yellow through orange, red, and purple, depending on the number of conjugated bonds. Several yellow pigments found in plants possess the conjugated polyene structure. The principal coloring matter in carrots is β -carotene which has the structure



Examination shows that this molecule contains the carbon skeletons of eight isoprene molecules, with 11 double bonds in a conjugated system. β -carotene and two isomers and a number of related compounds found in plants and animals are known collectively as *carotenoids*. They account for the color of tomatoes, egg yolk, yellow corn, etc., and for the yellows and browns exhibited by leaves and grasses in autumn after the green coloring matter (chlorophyll) has been withdrawn. Green leaves also yield β -carotene when extracted with fat solvents.

Vitamin A is a substance which cannot be synthesized in the animal body (cf. vitamins, Secs. 27-11ff) but is required in small amounts by man

and other animals. It is essential to normal growth, resistance to certain skin infections, and efficient functioning of the eyes; "night blindness" is one symptom of a deficiency. The nutritional requirement is usually met by that present in milk, butter, and eggs, and that provided by the carotene of green and yellow vegetables, which the animal body is able to convert into the vitamin. Fish, also, are able to use the carotinoids of their plant food for conversion to vitamin A, which is stored in their livers. The chief source for medicinal purposes has long been the oils from halibut and cod livers. Very considerable quantities of vitamin A are now produced synthetically from relatively simple compounds through a series of about 12 reactions (cf. Sec. 15-18). Synthetic vitamin A acetate (an ester formed by reaction between acetic acid and the hydroxyl group of the vitamin) is available commercially in the form of pure crystals; these come coated with gelatin to protect them from air because the highly unsaturated compound is easily destroyed by oxidation. Karrer established the following formula:

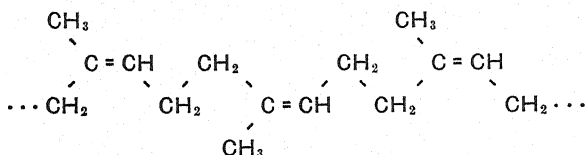


4.14 Rubber (caoutchouc) is the most important polyterpene. Its industrial source is *latex*, the sap of a tree (*Hevea brasiliensis*) cultivated on large plantations in the Malay Peninsula and the East Indies. As it exudes from the tapped trees, latex is a milky fluid containing 27 to 41 per cent of the unsaturated hydrocarbon *caoutchouc*, in the form of an emulsion in water protected by small amounts of resins and proteins. The diameters of the droplets range from 0.5 to 4 microns,¹ and they exhibit strong Brownian movement. These droplets are negatively charged, owing to OH ions taken up by the protective film of protein. To preserve latex better for shipment, ammonia is added. Acids, on the contrary, cause a rapid coagulation and the squeezing out of water. Most of the rubber shipped into this country is in the form of crepe rubber, coagulated by the addition of acetic or formic acid.

Caoutchouc is a hydrocarbon represented by the formula $(\text{C}_5\text{H}_8)_n$. On distillation, isoprene is one of the products of decomposition; conversely, isoprene is polymerized by various agents to a product that appears to be identical with natural rubber. Both chemical and X-ray

¹ One micron (μ) = 1×10^{-4} cm = 1×10^4 Å.

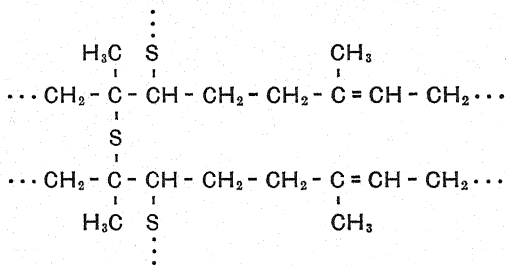
evidence shows that the latter is composed of very long chains, formed by repetition of the isoprene unit, as indicated below:



Values ranging between approximately 130,000 and 400,000 have been obtained for the average molecular weight; the latter figure corresponds to the union of about 6000 isoprene molecules.

Like other compounds containing double bonds, rubber is easily oxidized and reacts by addition with many other substances. The reaction of outstanding importance is the addition of *sulfur*.

Vulcanization. The great value of rubber lies in its remarkable mechanical properties, such as elasticity and resistance to rupture and abrasion. Native rubber loses these properties rather quickly; it becomes sticky when warm and hardens and cracks when cold. Industrial applications date from Goodyear's discovery (1839) of the vast improvement that results when it is heated with sulfur and small amounts of metallic oxides. The chemistry of vulcanization is still not entirely clear. One theory is that the addition of sulfur at double bonds results in cross linkages between the chains of neighboring molecules, somewhat as follows:



The formation of such a three-dimensional structure may account for the favorable changes in physical properties which result from vulcanization.

The process of vulcanization and most of what is stated in this section concerning the uses of natural rubber apply equally to "synthetic" rubber (Sec. 6-17).

4-15 Manufacture of Rubber Goods. The conversion of crude rubber into tires, shoes, and many other finished products is one of the most extensive of modern industries. Naturally, the procedure for different products varies in many details, but certain fundamental operations are almost universal.

After careful washing, crude rubber is subjected to a prolonged working between rollers (*milling*) during which time flowers of sulfur and other compounding ingredients are added and uniformly distributed; probably a certain amount of superficial oxidation is also involved and contributes to the marked improvements resulting from milling. The plastic mass is then molded into any desired form, usually in contact with cords or cloth, and is vulcanized by steam heating. The inclusion of the various chemical substances known as *compounding ingredients* is responsible for the high-grade products now manufactured. It must be admitted, however, that rubber manufacture is a highly developed art which has progressed chiefly by the method of trial and error; chemical theory still lags far behind practical applications. But chemical substances other than sulfur are now added for three distinct purposes, as follows:

Reinforcing and Softening Agents. Zinc oxide and certain clays have long been incorporated in rubber because they were observed to reinforce and strengthen the product. The outstanding development in producing the tires of today, with their high resistance to abrasion, is the incorporation of large amounts of *carbon black*. Oleic acid is the most important softening agent; this acts, presumably, by forming salts with the basic oxides (*e.g.*, zinc oleate) that dissolve in the rubber substance.

Vulcanizing Accelerators. The rate at which pure rubber and sulfur combine is very slow even at high temperatures. It was early recognized that the reaction was favored by the inclusion of metallic oxides, and they have long been added for this purpose. Much more important is the effect of certain organic compounds of nitrogen. Rapid development along this line has made available a large variety of vulcanizing accelerators, some of which are effective even without heating.

Antioxidants. The deterioration of rubber on standing, as evidenced by hardening and surface cracking, appears to be due largely to atmospheric oxidation. Various substances that retard such changes, known as *antioxidants*, are now incorporated.

The manufacture of "rubber-processing chemicals," for the most part accelerators and antioxidants, is one of the important subdivisions of the synthetic chemicals industry.

Latex Products. By the addition of ammonia the coagulation of latex can be prevented and, by centrifuging or otherwise, the natural 35 per cent of solids can be increased to about 70 per cent while preserving the colloidal dispersion. Considerable amounts of this preserved concentrated latex are now used for the production of thin rubber goods (*e.g.*, surgeons' gloves) and for coating metallic grids and other objects of irregular shape. This may be done either by dipping or by electrodeposition, taking advantage of the negative charges on the droplets of latex. *Lastex* is latex thread wrapped with silk, cotton, or nylon and woven into elastic fabrics.

4-16 Alicyclic Compounds. The closed-chain compounds described in this chapter are called *alicyclic*. This word is compounded from *cyclo*, suggesting the ring structure, and the prefix *ali* from aliphatic, the comprehensive name for all open-chain compounds.

The term alicyclic is intended to call attention to the close resemblances between these ring compounds and the corresponding classes of open-chain hydrocarbons. Comparison shows very definitely that *ring formation, as such, produces no essential change in chemical properties*. The cyclanes, in which carbon atoms are joined by single bonds only, are fully saturated compounds which closely resemble the alkanes. Five-mem-

bered and larger rings are extremely stable. The terpenes and other unsaturated cyclic hydrocarbons behave like the alkenes and alkadienes, from which we conclude that there is no essential difference in a double bond between carbon atoms of a ring and those of an open chain. Because all double bonds are rather easily split by oxidants, the carbon rings of unsaturated alicyclic compounds are much less stable than those of typical cyclanes.

Questions

1. Write structural equations for the reactions between metallic sodium and (a) 1,2-dibromohexane; (b) 1,6-dibromohexane. Name the products, state the relation between them, and compare their chemical properties.

2. (a) Show why ring formation is the only plausible explanation of the fact that a *saturated* compound, containing not over five carbon atoms and no bromine, is formed when sodium acts on 1,5-dibromopentane. (b) Suggest an explanation of the fact that the yield of cyclopentane is low.

3. Write structural equations for the probable action of sodium on the following compounds and name the products: (a) 1,5-dibromohexane; (b) 1,6-dibromo-3,4-dimethylhexane.

4. Write the structural formulas of the following compounds and state with what open-chain compounds each is isomeric: (a) 1,3-dimethylcyclopentane; (b) 1-methyl-4-ethylcyclohexane.

5. Explain fully, in terms of the tetrahedral carbon atom, why rings of five and six carbon atoms are formed more readily than others.

6. Explain fully, in terms of the strain theory, why rings of three and four carbon atoms are less stable than those of five or six.

7. Suggest an explanation of the fact that rings of eight and more carbon atoms are formed with difficulty, although when formed they are quite stable.

8. Show that dimethylcyclopropane is isomeric with cyclopentane. Tell how you could distinguish between them by qualitative chemical tests.

9. Cyclobutane will add two atoms of bromine, though not easily. Write the structural formula of the product, name it, and show how it differs in structure from the bromine addition product of 1-butene.

10. A pure substance which shows all the properties of a saturated hydrocarbon is subjected to a quantitative analysis and the percentages of carbon and hydrogen are determined. Explain accurately why it would still be difficult to prove with certainty whether it is the alkane $C_{18}H_{38}$ or a cyclane, $C_{18}H_{36}$.

11. Give the general formulas of the cyclanes, the cyclenes, and the cyclodienes. With what class or classes of open-chain compounds is each series isomeric?

12. The formula of a hydrocarbon is known to be C_6H_8 . Is that sufficient information on which to predict how many atoms of bromine it will add? Explain fully.

13. What evidence is there, if any: (a) That single bonds between carbon atoms in (five- or six-membered) rings are any more easily severed than linkages between carbon atoms in normal paraffin chains? (b) That double bonds between carbon atoms in closed chains differ in any essential properties from those between carbon atoms of open chains? (c) That ring closure, of itself, produces any material change in chemical properties?

14. Starting with 1,6-dibromohexane, write structural equations for the reactions by means of which the following compounds could be successively prepared: (a) cyclo-

hexane; (b) bromocyclohexane; (c) cyclohexene; (d) dibromocyclohexane; (e) a cyclohexadiene.

15. Show how dipentene could be formed from two molecules of isoprene if one of these reacts by 1,4-addition and the other by 1,2-addition.

16. Write possible structural formulas for two terpenes of each class and show for each of them why the molecular formula is $C_{10}H_{16}$ and not $C_{10}H_{22}$.

CHAPTER 5

AROMATIC HYDROCARBONS

In previous chapters we have studied and compared the open-chain aliphatic hydrocarbons and certain ring compounds described as alicyclic. There remains to be considered another—very important—class of closed-chain compounds called *aromatic*. The simplest of these is benzene, to which all the others are related.

The term *aromatic* (Gr., *aroma*, spice) arose from the fact that some of the compounds related to benzene that were first isolated and examined had pleasant spicelike odors. We now know that odor—whether pleasant or the contrary—is not a characteristic property of all such substances. Nevertheless, the word is retained for convenience in distinguishing them from aliphatic and alicyclic compounds.

BENZENE

5-1 Benzene is isolated in large quantities from coke-oven gas and tar (Sec. 6-23) and is produced also by the chemical conversion of petroleum hydrocarbons (Sec. 6-18). It is a colorless liquid of rather pleasant odor but poisonous properties. Like all other hydrocarbons it is practically insoluble in water and water solutions but freely miscible with many organic liquids. Comparison of its physical constants with those of six-carbon compounds of other series (Table 5-1) shows that benzene most closely resembles cyclohexane, though its density and refractive index are notably higher.

TABLE 5-1 STRUCTURE AND PHYSICAL PROPERTIES; CONSTANTS FOR BENZENE AND CORRESPONDING HYDROCARBONS OF OTHER SERIES

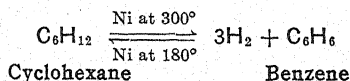
Hydrocarbon	Melting point, °C	Boiling point, °C	Density, grams per ml, 20°C	Refractive index, n_D^{20}
C ₆ H ₆ , benzene (aromatic series).....	+5.5	80.1	0.8790	1.5011
C ₆ H ₁₂ , cyclohexane (cyclo series)...	+6.6	80.7	0.7786	1.4262
C ₆ H ₁₂ , 1-hexene (alkene series).....	-139.	63.6	0.6734	1.3876
C ₆ H ₁₄ , <i>n</i> -hexane (alkane series).....	-95.3	68.7	0.6594	1.3749

Benzene is the raw material for producing a very large number of other aromatic compounds, both in the laboratory and industrially (Chap. 23). It is also an effective solvent and a desirable component of motor fuel.

5-2 Chemical Properties. Benzene shows a combination of chemical properties which sets it aside from the hydrocarbons of all other series. It resembles hexane and cyclohexane in that it is not easily oxidized, does not polymerize, and usually reacts by substitution with chlorine and bromine; but it differs from hexane and cyclohexane by reacting readily—again to yield substitution products—with nitric acid, sulfuric acid, and certain other reagents. Benzene differs further from all saturated hydrocarbons in *sometimes* forming addition products (*e.g.*, with hydrogen, chlorine, and ozone) like a compound containing three double bonds. But, as already noted, it differs sharply from any unsaturated aliphatic or alicyclic compound in its resistance to oxidation, in its failure to polymerize, and in its usual pattern of reaction by substitution rather than addition.

This unexpected combination of properties is characteristic of aromatic compounds in general.

5-3 The Benzene Ring. Benzene is formed from cyclohexane when the vapors of that hydrocarbon are led over nickel at about 300°C. Furthermore, when the vapors of benzene are mixed with hydrogen and passed over the same catalyst at about 180°C, six atoms of hydrogen are added and cyclohexane is regenerated:

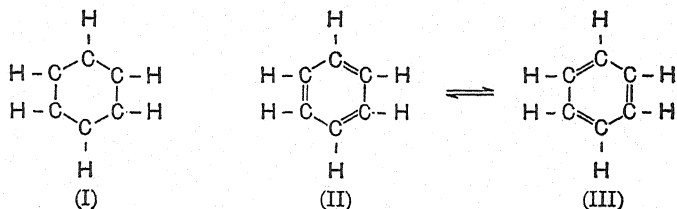


These relations strongly suggest that the six carbon atoms in benzene form a closed chain, or ring, as they are known to do in cyclohexane. This inference is supported by a mass of other evidence, so complete and so convincing that it need not be presented in detail.

The intensive study of benzene substitution products has further established that one hydrogen atom is attached to each carbon and that these hydrogen atoms are fully equivalent so that, no matter which one is replaced by another atom or group, the same product is obtained. This means that the benzene molecule must be *symmetrical*.

These conclusions from the methods and logic of classical organic chemistry have been fully substantiated by recent, more direct physical methods (diffraction of X rays and electrons) which, furthermore, have added the following details: (1) the six carbon and six hydrogen atoms lie in a plane; (2) lines joining the carbon atoms form a *regular* hexagon; and (3) the distance between every pair of adjacent carbon atoms is the same.

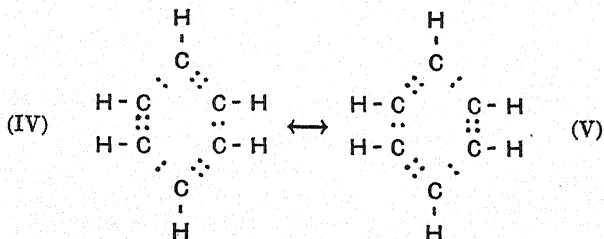
Formula (I) pictures adequately these known relative positions of the atoms in a molecule of benzene but is obviously incomplete in that it leaves unaccounted for one valence of each carbon atom.



Of the many ways which have been suggested to account for these "missing" valences, the formula proposed by August Kekulé¹ in 1865 is the oldest and still the most widely used. Kekulé assumed that the six unaccounted-for valences unite in pairs to form three double bonds. Later, other facts led him to add the assumption that these bonds are in rapid oscillation between the positions shown in (II) and (III); in other words, that each pair of carbon atoms is joined, now by a single and now by a double bond, in rapid alternation.

The obvious objection to the Kekulé formula is its failure to explain the low chemical reactivity of the double bonds which it assumes. Why is benzene not more inclined to react by addition like an alkene or a terpene? A partial answer was found in the *conjugation* of these bonds. It has been noted already that an open-chain conjugated system tends to act as a unit, with reactive points at its ends—as shown, for example, by the phenomenon of 1,4-addition. Benzene contains a *closed* conjugated system which has no "ends" or points of special reactivity.

5.4 Resonance. In the most recent view, Kekulé's valence bonds are replaced by pairs of electrons, as suggested by (IV) and (V). These, of course, are nothing more than (II) and (III) dressed up in modern clothes.



¹ It should be recorded also that Kekulé was the first to visualize the possible existence of carbon *rings* and to propose the cyclic structure for benzene. With the facts then available, this was hardly more than an inspired—very brilliant—guess. It was not until many years later that chemists learned of cyclohexane and its relations to benzene, referred to above, and obtained the physical evidence which now supports the ring structure.

But the concept of resonance goes much further. Instead of regarding benzene as *oscillating* between the two Kekulé forms—now one, now the other—the molecule is regarded as a *resonance hybrid*¹ with a *single* structure which partakes of both.

This implies that the ring electrons are distributed uniformly among the six carbon atoms so that the bond between any pair of them is neither single nor double, but something in between. (For want of a better name, this might be called a “benzene” bond.) Direct supporting evidence has been furnished by X-ray spectroscopy which shows clearly that all six of the ring bonds have the *same* length, 1.39 Å. This value lies between the 1.54 Å for the C:C bond and the 1.34 Å for the C::C bond observed in aliphatic and alicyclic molecules.

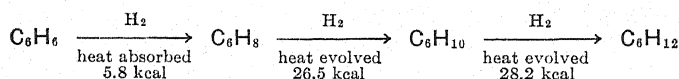
Symbols for Resonance. It is impossible to write any single structural formula which represents adequately the structure of a hybrid molecule. (The suggestion of writing a “benzene bond” as three dots, to indicate three electrons, is objectionable for various reasons.) The best we can do is to write an ordinary formula for each of the *contributing forms*—of which there may be more than two—and place between them an arrow of the type \longleftrightarrow , as is done above between (IV) and (V). It must be understood clearly that this style of arrow signifies something quite different from the ordinary double arrows, \rightleftharpoons , used to indicate reversible changes.

5-5 Resonance Energy. There are many compounds for which it is possible to write more than one reasonable² formula differing only in the average positions of electrons. Any such molecule must be regarded as a resonance hybrid with an intermediate actual structure. Aside from abnormal bond lengths, such compounds are characterized by a total energy content lower than expected. The molecular heat of combustion of benzene, for example, is about 39 kcal less than that calculated on the assumption that it contains three C:C and three C::C bonds. (“Normal” values for such bonds are determined by measurements on non-resonating molecules.) This difference is called the resonance energy. *Resonance energy tends to stabilize a molecule against any change which*

¹ The meaning of this concept can be made clearer by an analogy. “A mule is a hybrid between a horse and a donkey. This does not mean that some mules are horses and the rest are donkeys, nor does it mean that a given mule is a horse part of the time and a donkey the rest of the time. Instead, it means that a mule is a new kind of animal, neither horse nor donkey, but intermediate between the two and partaking to some extent of the character of each.” (Quoted by permission from G. W. Wheland, “The Theory of Resonance,” John Wiley and Sons, Inc., New York, 1944.)

² Resonance formulas cannot be considered “reasonable” unless they correspond to virtually the same relative positions of all atomic *nuclei*. The positions of electrons may vary more, but not too widely; in general, the octet rule must be maintained. We will consider later what forms, within these limitations, are most probable and make the major contributions to the actual state of a hybrid molecule.

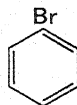
would destroy its hybrid structure—it is a measure of the energy which must be supplied from outside for such a purpose. Any *addition* to the benzene ring destroys its hybrid structure and, for this reason, is difficult. Direct evidence on this point is found in measurements on the heat of hydrogenation of benzene. The addition of hydrogen to a double bond is ordinarily an exothermic reaction, but it has been shown that the addition of *one* molecule of hydrogen to benzene—the step which destroys the resonating system—is effected only with great difficulty and *absorbs* heat (5.8 kcal per mole). The product, cyclohexadiene, readily adds two more molecules of hydrogen with the usual evolution of heat:



5-6 Benzene Nucleus. The structure which is common to all compounds classified as *aromatic* is an unsaturated six-carbon ring stabilized by resonance as in benzene. This is conveniently described as the benzene, or aromatic, *nucleus*. We shall see later that there may be attached various carbon side chains, or other atoms and groups, and that molecules may contain more than one such nucleus either independent or condensed.

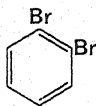
Most of the chemical reactions of benzene and other aromatic compounds result in the exchange or alteration of groups attached to the nucleus. The latter passes apparently unchanged from one compound to another, retaining its resonating structure and the characteristic properties resulting therefrom. For this reason it is usually unnecessary, when writing structural equations for reactions, to define the nuclear structure in detail. Instead it is customary—because it is timesaving and convenient—to use a conventional symbol.

Conventional Formulas. Benzene is usually represented by a hexagon—supposedly regular but sometimes elongated for typographical convenience—with alternate double and single bonds as in a Kekulé formula:

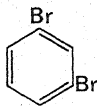
Benzene, C_6H_6 Bromobenzene, $\text{C}_6\text{H}_5\text{Br}$

This conventional symbol stands for the benzene molecule C_6H_6 ; that is, each of its six angles represents a carbon atom and an attached hydrogen atom. In other aromatic compounds, such as bromobenzene, atoms or groups substituted for hydrogen are indicated by writing their symbols in appropriate positions about the hexagon; a hydrogen atom is implied at each angle where no substituent is shown.

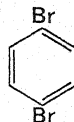
5.7 Naming Benzene Derivatives. There are thousands of aromatic compounds that may be thought of as formed from benzene by replacing one or more of its six hydrogen atoms by other atoms or groups. When a *single* hydrogen atom is thus replaced, no isomers are possible; for example, there exists only one compound of the composition C_6H_5Br and this can be described simply as bromobenzene. But when *two* hydrogen atoms are replaced, *three*—and *only* three—position isomers are always possible.¹ For example, there are known three compounds of the formula $C_6H_4Br_2$, differing in the relative positions of the bromine atoms, as follows:



1,2-Dibromobenzene
(*ortho*)
m.p. 1.8°



1,3-Dibromobenzene
(*meta*)
m.p. -6.9°



1,4-Dibromobenzene
(*para*)
m.p. 89°

In referring to such isomers, it is most convenient to number the carbon atoms of the ring (or the angles of the conventional hexagon) and name the compounds accordingly. By custom the symbol of one substituent is written or printed at the top; the numbering starts here and proceeds clockwise as illustrated.

Ortho, *meta*, and *para* (and the abbreviations, *o*-, *m*-, and *p*-) are prefixes often used instead of the numbers to indicate the 1-2, the 1-3, and the 1-4 positions, respectively; thus, the names *o*-dibromobenzene and 1,2-dibromobenzene refer to the same compound. With three or more substituents, positions should be indicated *always* by numbers.

5.8 Orientation. The structural theory and the symmetry of benzene explain why there should be three and only three dibromobenzenes, $C_6H_4Br_2$. There remains to be considered how we know which structure to assign to each of the three compounds the melting points of which are listed above. This can be explained rather

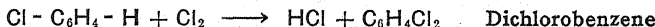
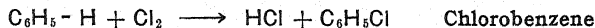
¹ A mechanical analogy will help to make clear *why* there are three but only three isomers when any two hydrogen atoms are replaced. Remembering that the benzene molecule is perfectly *symmetrical*, we may compare it with a wheel with six spokes symmetrically placed. Imagine a large number of such wheels. If any *one* spoke of each be painted, the wheels remain identical; by rotation they may be made to correspond exactly, part for part. But suppose a number of people are instructed to paint one additional spoke of each wheel, selecting them at random. Some would paint a spoke immediately to the right or left of the one already painted; others would skip one—either to the right or left; still others would select the spoke directly opposite the first. At the end, there would appear to be five different combinations, but by rotation some would be found identical. Actually, it would be possible to separate the wheels into three piles; those in each pile would be identical but those from different piles could not be so turned that their painted spokes would coincide.

simply with respect to one of them. If the bromine atoms are *para*, only one trisubstitution product can be formed if an H atom is replaced by Y, because, in the *para* compound, positions 2,3,5, and 6 are equivalent and the product will be identical no matter where Y enters. Since the compound $C_6H_4Br_2$ which melts at $89^\circ C$ has been shown to yield only one substitution product of the type $C_6H_3Br_2Y$, it must be the *para* isomer. The same method may be applied to the other two isomers but becomes more complicated.

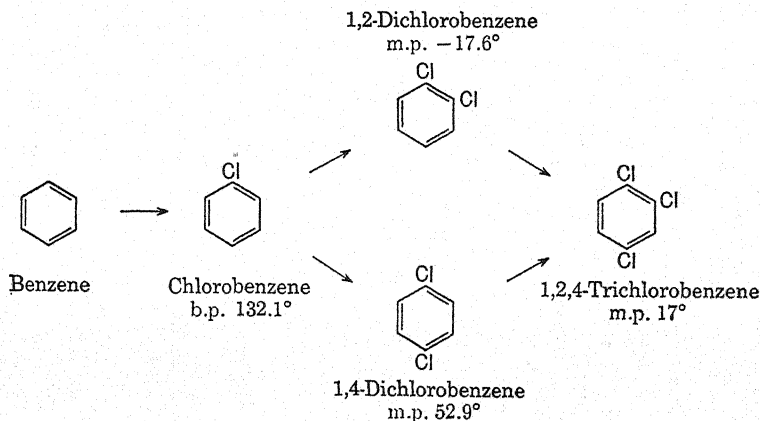
The example given illustrates the fundamental principle of what is known as Körner's absolute method of orientation. Körner (1874) applied it—with a vast amount of experimental work—to establishing the structures (*ortho*, *meta*, or *para*) of various benzene disubstitution products.

REACTIONS OF BENZENE

5.9 Halogenation. Benzene reacts very slowly with pure chlorine or bromine, but in the presence of iron, and of some other catalysts, energetic reaction occurs. Halogen acid—HCl or HBr—is evolved freely, indicating reaction by substitution, and analysis of the organic products shows that an atom of hydrogen is removed for each atom of halogen entering the molecule, *e.g.*,



If, in practical chlorination, the temperature is kept around $0^\circ C$, the product is almost pure chlorobenzene. Higher temperatures yield a mixture of 1,2-dichlorobenzene and 1,4-dichlorobenzene, with a very little of the 1,3 or *meta* isomer. Each of the former yields 1,2,4-trichlorobenzene by further reaction with chlorine:



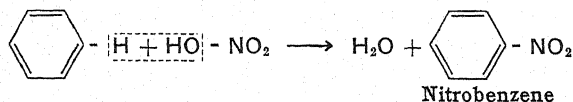
Under similar conditions bromine yields substitution products of the corresponding structures. Iodine also can be introduced by direct sub-

stitution (which is not true in the aliphatic series) but much less readily than chlorine and bromine.

The addition of chlorine to benzene is described in Section 23-2.

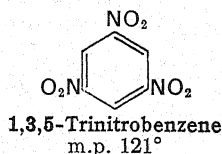
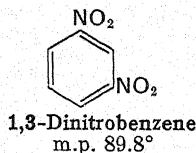
5-10 Nitration; Nitro Compounds. The replacement of a hydrogen atom of an organic compound by a nitro group, NO_2 , is called nitration; its products are *nitro* compounds. This is one of the most important reactions in the aromatic series. It is usually effected by the action of so-called *mixed acid*—a mixture of concentrated nitric and sulfuric acids, the composition of which may be varied at will. The sulfuric acid is added to take up water formed in the reaction and thus maintain the effective concentration of the nitric acid.

Benzene reacts readily with mixed acid. Below 40°C the product is almost exclusively the monosubstitution product, nitrobenzene:



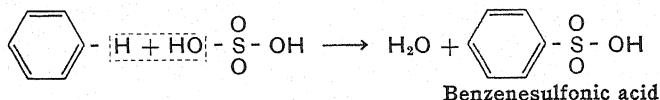
Nitrobenzene is a faintly yellow, highly refractive liquid (m.p. 5.7°C ; b.p. 210.9°C ; d , 1.207) which darkens on exposure to light. It is practically insoluble in water and in all water solutions (including sodium hydroxide) but is freely miscible with most organic liquids and with sulfuric acid. Large quantities are manufactured by nitrating benzene and used, mainly, for reduction to aniline, $\text{C}_6\text{H}_5\text{NH}_2$.

At temperatures around 100°C mixed acid converts nitrobenzene almost quantitatively into *m*-dinitrobenzene, a pale yellow crystalline solid. The introduction of a third nitro group is very difficult. Prolonged heating of *m*-dinitrobenzene with a large excess of mixed *fuming* nitric and sulfuric acids (extreme conditions) gives a low yield of 1,3,5-trinitrobenzene; but, although the latter is a useful military explosive, it has not been possible to produce it except by an indirect method. In summary, each nitro group in the molecule makes it more difficult to introduce another (Sec. 22-8).



5-11 Sulfonation; Sulfonic Acids. When heated with concentrated sulfuric acid or when shaken with cold fuming sulfuric acid, benzene dissolves. If the reaction mixture is cooled and then diluted by pouring on to ice, a solid separates. This is *benzenesulfonic acid*, formed by a reac-

tion in which the SO_2OH group substitutes a hydrogen atom of benzene and establishes a direct linkage between sulfur and carbon:

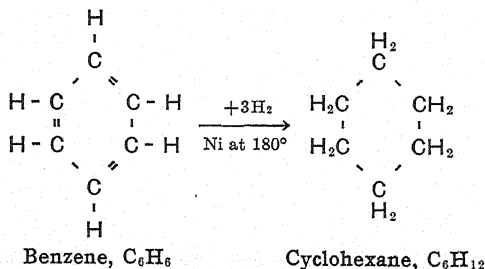


Benzenesulfonic acid is very soluble in water but can be isolated in the form of colorless crystals (containing water of hydration) which melt at 43 to 44°C. In solutions it functions as a strong acid because the hydrogen atom of the SO_2OH group is highly ionized; it neutralizes bases, forming salts known as sulfonates, *e.g.*, $\text{C}_6\text{H}_5\text{SO}_2\text{O}^-\text{Na}^+$, sodium benzenesulfonate.

When benzenesulfonic acid is heated at 225 to 250°C with excess of strong sulfuric acid and sodium sulfate, a second SO_2OH replaces hydrogen and 1,3-benzenedisulfonic acid is formed. It is very difficult to introduce a third SO_2OH group; when this happens, it enters *meta* to each of the groups already present, yielding 1,3,5-benzenetrisulfonic acid.

The substitution of hydrogen by the SO_2OH group, with formation of a direct carbon-sulfur linkage, is known as *sulfonation*. Like nitration, this is an important and characteristic reaction of aromatic compounds in general.

5.12 Hydrogenation; Sabatier Reaction. Benzene does not react with nascent hydrogen and was long regarded as incapable of forming addition products with this element. Direct addition was accomplished by Sabatier¹ and his associates in 1901 by passing hydrogen saturated with the vapors of benzene over finely divided nickel at about 180°C. As conducted in this way, *three* molecules (six atoms) of hydrogen are always added:



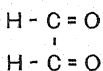
The hydrogenation of organic compounds in the vapor phase with the aid of finely divided metallic catalysts, especially nickel, is known as the Sabatier reaction. It is a general method for adding hydrogen to the nucleus of aromatic compounds and is used industrially for the hydrogenation-

¹ See footnote 2, page 128.

tion of benzene, naphthalene, phenol, etc. A modified form is used on a much larger scale in the so-called *hardening* of fatty oils (Sec. 16-23).

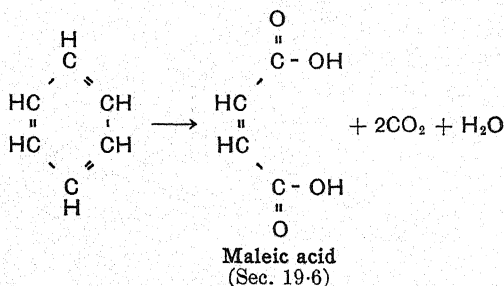
5-13 Oxidation. Benzene is not oxidized by permanganate solutions or by dichromic acid or nitric acid. This resistance of the nucleus to oxidizing agents is another property characteristic of most aromatic compounds.

Except at high temperatures, as described below, the one effective oxidizing agent is *ozone*. This does not react easily, but it is possible to obtain a *triozonide*, $C_6H_6(O_3)_3$, as from an open-chain compound containing three double bonds. When this ozonide is treated with water (cf. Sec. 3-13), it is split into three molecules of the dialdehyde glyoxal:

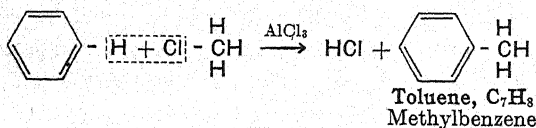


Combustion. Liquid benzene burns in air with the formation of much soot. When the vapors are mixed with a suitable proportion of air, they burn smoothly to carbon dioxide and water. Benzene and other aromatic hydrocarbons have excellent antiknock properties and for this reason are desirable components of motor fuels.

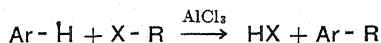
Catalytic Oxidation. Benzene is oxidized industrially for the manufacture of maleic acid by passing its vapors, mixed with a suitable proportion of air, over vanadium pentoxide, V_2O_5 , at a temperature carefully maintained between 400 and 450°C. Under these conditions the ring is opened, two carbon atoms are eliminated as carbon dioxide, and each end of the remaining four-carbon chain is oxidized to the carboxyl group, COOH:



5-14 Friedel-Crafts Reaction. Benzene reacts with alkyl halides in the presence of anhydrous aluminum chloride, *e.g.*,



This illustrates a general method for substituting *nuclear* hydrogen atoms by alkyl radicals. It is known as the Friedel-Crafts reaction. Since with rare exceptions *only* nuclear hydrogen can react in this way, ability to enter into the reaction is another characteristic property of aromatic compounds. The type equation is:



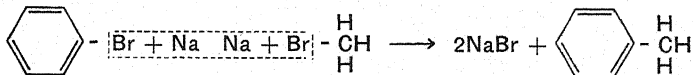
in which ArH represents any aromatic compound and RX an alkyl halide, preferably a chloride.

A disadvantage of the Friedel-Crafts reaction as applied to preparing alkylated benzenes is that it does not stop with the replacement of one hydrogen atom. For example in preparing toluene by the reaction shown above, considerable amounts of dimethylbenzenes are formed also. This is because the remaining nuclear hydrogen atoms become more reactive after one methyl group has been introduced. Another limitation is that alkyl radicals larger than ethyl are apt to be isomerized (Sec. 6·8) by anhydrous aluminum chloride.

The scope of the Friedel-Crafts reaction is much broader than is indicated above. Instead of an alkyl chloride one may use *any* organic chloride except those of the types of vinyl chloride (Sec. 15·5) and chlorobenzene (Sec. 7·20). Acid chlorides, acid anhydrides, and alkenes may also be used as alkylating agents. The original catalyst, anhydrous AlCl_3 , can be replaced sometimes by other anhydrous chlorides such as FeCl_3 and SnCl_4 . Another variation uses anhydrous HF , 96 per cent H_2SO_4 , or other highly concentrated acid. The mechanism of the Friedel-Crafts reaction is discussed in Section 22·5.

HOMOLOGUES OF BENZENE

5·15 Toluene, C_7H_8 , is methylbenzene. This structure is established by several methods of laboratory synthesis including the Friedel-Crafts and the Wurtz-Fitting reactions, *e.g.*,



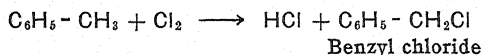
Toluene is recovered in large quantities from coke-oven gases and is manufactured in even larger amounts from petroleum (Sec. 6·18). It resembles benzene in most physical properties, but is less poisonous. That quality and the somewhat higher boiling point (110.6°C) make it preferred as an industrial solvent, and large quantities are used for this purpose.

The chemical properties of toluene divide themselves naturally and rather sharply into those which involve hydrogen atoms attached to the nucleus (*nuclear hydrogen* atoms) and reactions that involve the methyl *side chain*.

Nuclear Reactions. The nuclear hydrogen atoms in toluene can be replaced like those of benzene by halogenation in the presence of iron, by nitration, by sulfonation, and by the Friedel-Crafts reaction. The most important of these reactions is nitration, which yields the military high explosive TNT, or 2,4,6-trinitrotoluene (Sec. 24·2). The *nucleus* is highly resistant to oxidation. It adds three molecules of hydrogen in the Sabatier reaction, forming methylcyclohexane, $C_6H_{11} \cdot CH_3$.

Side-chain Reactions. The hydrogen atoms of the methyl side chain in toluene resemble those of methane in that they are *not* replaceable by nitration, sulfonation, or the Friedel-Crafts reaction. The principal reactions in which they are involved are oxidation (Sec. 5·17) and halogenation.

In the absence of iron and other catalysts favoring *nuclear* substitution, one, two, or all three of the side-chain hydrogen atoms in toluene can be replaced by chlorine or bromine, *e.g.*,



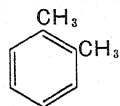
Reaction proceeds best at the boiling point of toluene and is favored by short-wave radiation from direct sunlight or a mercury lamp. It must be emphasized that the presence or absence of iron or a similar catalyst is the principal factor in determining whether the halogens will substitute nuclear or side-chain hydrogen atoms.

5·16 Higher Homologues of Benzene. Toluene is the simplest of many hydrocarbons that may be regarded as derived from benzene by replacing one or more of its hydrogen atoms by as many alkyl groups (methyl, ethyl, isopropyl, etc.). Each such compound consists, therefore, of one six-carbon aromatic nucleus with one or more saturated side chains attached. Collectively, they form a homologous series of the general formula C_nH_{2n-6} . General methods for their laboratory synthesis are the Wurtz-Fittig,¹ the Friedel-Crafts, and the Grignard syntheses (Sec. 7·16). Those of commercial importance are obtained as indicated below.

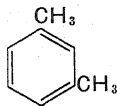
Xylenes, or dimethylbenzenes, are recovered in commercial quantities from coke-oven gas and tar. A mixture of the three isomers thus obtained is called *solvent naphtha*. Much larger quantities are now produced as a co-product of manufacturing toluene from petroleum hydro-

¹ It has been mentioned (Sec. 2·9) that the Wurtz-Fittig reaction is of little practical value when applied to a mixture of two *alkyl* halides because it leads to a mixture of products hard to separate. This objection is less serious in preparing benzene homologues. Thus in forming toluene (b.p. 110.6°C) by the action of sodium on a mixture of bromobenzene and methyl bromide the by-products are ethane (a gas) and biphenyl, $C_6H_5 \cdot C_6H_5$, which boils at 254.9°C; such a mixture is easily separated.

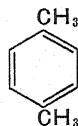
carbons (Sec. 6·18). The mixture is useful as an industrial solvent and in high-octane motor fuels. It is now being fractionated into its components and the individual xylenes used for oxidation to their corresponding acids (Sec. 24·10).



o-Xylene
b.p. 144.4°
m.p. -25.2°



m-Xylene
b.p. 139.1°
m.p. -47.9°



p-Xylene
b.p. 138.3°
m.p. 13.3°

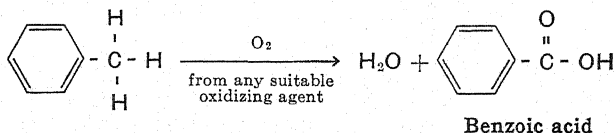
Ethylbenzene (b.p. 136.2°C) is manufactured on a large scale by the catalytic addition of ethylene to benzene. It is used almost entirely for dehydrogenation to *styrene*, $C_6H_5.CH=CH_2$. These reactions are described in Section 23·4. Styrene is required for the manufacture of GR-S synthetic rubber and polystyrene plastics.

Cumene (b.p. 152.4°C) is isopropyl benzene. It has been manufactured by the catalytic addition of benzene to propene for use as a component of high-octane aviation fuel.

p-Cymene (b.p. 177.1°C), 1,4-methylisopropylbenzene, has the same carbon skeleton as *p*-menthane (Sec. 4·3) and many terpenes. It is obtained in considerable quantities from spruce turpentine and from the wash waters of sulfite pulp manufacture.

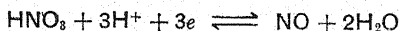
All the homologues of benzene exhibit the two sets of chemical reactions—nuclear and side-chain—already illustrated by toluene. Side-chain oxidation is the only one which requires special mention.

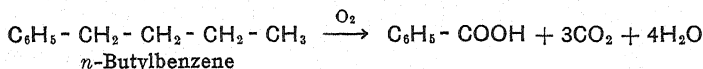
5·17 Oxidation of Side Chains. When a benzene homologue is refluxed with dilute nitric acid,¹ or dichromic acid, or alkaline permanganate solutions, the nucleus is not affected but the side chains are oxidized to carboxyl groups; *e.g.*,



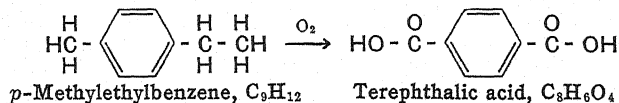
Benzoic acid is likewise the product when any other benzene homologue with a *single* side chain is oxidized, *e.g.*,

¹ When its *oxidizing* action is desired, nitric acid of density 1.15, containing about 25 per cent HNO_3 by weight, is generally used instead of the more concentrated nitric acid or mixed acid employed in nitrations. The partial equation for the reduction of nitric acid is

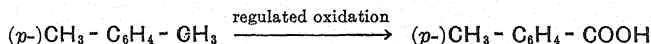




If the molecule contains *two or more* side chains, the usual product is an acid containing as many carboxyl groups directly attached to the nucleus as there were side chains in the original hydrocarbon, *e.g.*,



By careful regulation of the conditions it is sometimes possible to oxidize one side chain only, leaving another unaffected, *e.g.*,



The clean-cut oxidation of side chains to carboxyl groups is another property characteristic of aromatic compounds. It must be ascribed to an influence of the nucleus in activating hydrogen atoms on the side-chain carbon directly attached to it; oxidation appears to begin here and results in cleavage of the side chain at this point. Side chains in aliphatic and alicyclic compounds are no more sensitive to attack by oxidants than other parts of the molecules.

5.18 Directing Influences. In closing the discussion of benzene and its homologues, attention must be directed to another property common to aromatic compounds, which they illustrate. This relates to the position taken by a second atom or group, entering the molecule by substitution of nuclear hydrogen, *after one hydrogen atom of benzene has been replaced*.

A number of illustrations already given show that when a second hydrogen atom is substituted the three isomeric disubstitution products theoretically possible are *not* formed in equal quantities nor in the proportions to be expected from the law of chance.¹ Table 5-2 summarizes the results obtained by Holleman in a very careful set of experiments conducted under comparable conditions.

Summarizing the facts, it appears that any atom or group other than hydrogen, attached to a *nuclear* carbon atom, exerts a *directing influence* which is the chief factor in determining the position of further substitution. The chlorine atom is always *ortho*- and *para*-directing and whether chlorobenzene is further chlorinated, brominated, nitrated, or sulfonated

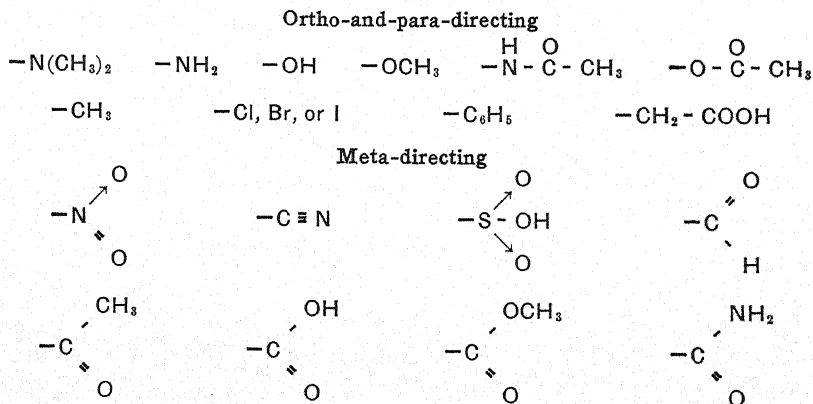
¹ In any benzene monosubstitution product, $\text{C}_6\text{H}_5\text{X}$, there are two hydrogen atoms *ortho* to X, two *meta* to X, and one *para* to X. If another atom or group, Y, enters by replacing hydrogen, the law of chance would therefore lead us to expect the mixture of isomers, $\text{C}_6\text{H}_4\text{XY}$, to contain the *o*-, *m*-, and *p*-compounds in the proportions of 2:2:1 or 40:40:20. Considering the *o*- and *p*-isomers together, this ratio becomes *o* + *p*:*m*::60:40. The last column in Table 5-2 shows how widely the facts differ from this prediction.

TABLE 5-2 DIRECTING INFLUENCES IN SUBSTITUTION

Compound studied	Substituting reaction	Percentage of isomers formed			Ratio <i>o</i> + <i>p</i> : <i>m</i> among products
		<i>Ortho</i>	<i>Meta</i>	<i>Para</i>	
C_6H_5Cl	Chlorination	39.0	6.0	55.0	94 :6
C_6H_5Cl	Bromination	11.2	1.6	87.2	98.4:1.6
C_6H_5Cl	Nitration	30.1	69.9	100.0:0.0
C_6H_5Cl	Sulfonation	100.0	100.0:0.0
$C_6H_5.CH_3$	Bromination	39.7	60.3	100.0:0.0
$C_6H_5.CH_3$	Nitration	56.0	3.1	40.9	96.9:3.1
$C_6H_5.CH_3$	Sulfonation	31.9	6.1	62.0	93.9:6.1
$C_6H_5.OH$	Chlorination	49.8	50.2	100.0:0.0
$C_6H_5.OH$	Bromination	9.8	90.2	100.0:0.0
$C_6H_5.OH$	Nitration	40.0	60.0	100.0:0.0
$C_6H_5.COOH$	Nitration	18.5	80.2	1.3	19.8:80.2
$C_6H_5.COOH$	Sulfonation	93.0	7.0	7.0:93.0
$C_6H_5.NO_2$	Nitration	6.4	93.2	0.25	6.7:93.2

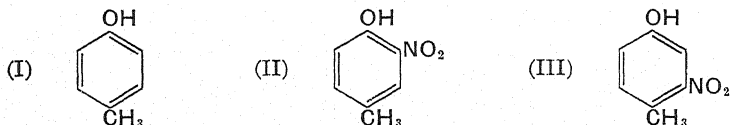
it is nearly always a hydrogen atom *ortho* or *para* to chlorine which is replaced; in only an occasional molecule does the second group enter in the *meta* position. Conversely, the NO_2 and SO_2OH groups are *meta*-directing.

5-19 The prevailing influences of the atoms and groups most often found in union with the benzene nucleus may be summarized¹ here for reference, as follows:



¹The Hammett and Illingsworth rule is a useful aid to memory: If YW is the substituent group, the next group substituting on the ring tends to go to the *meta* position if W is an element occurring in a *later* group than Y in the periodic table, or if W is an element with a *lower* atomic weight in the same periodic group; all other substituents tend to direct *ortho* and *para*.

The groups in each list are arranged roughly in the order of decreasing effectiveness. This order is established by experiments such as the following. The compound *p*-cresol (I) contains the groups OH and CH₃, both of which are of the *ortho*-and-*para*-directing type. There is no open position *para* to either, and any substituting atom or group must enter *ortho* to OH or to CH₃; *e.g.*, mononitration must yield either (II) or (III):



Experiment shows that (II) is formed almost exclusively, thus proving that the OH group exerts the more powerful directing influence.

5.20 Activating and Deactivating Groups. Under the same experimental conditions toluene is mononitrated—in the *ortho* or *para* position—fourteen times as rapidly as benzene. Similar results are obtained in other nuclear substitutions of toluene such as alkylation by the Friedel-Crafts reaction. This means that the methyl group in toluene not only *directs* an entering group to the *ortho* or *para* position but in some way *activates* these positions so that hydrogen atoms are more easily replaced. Such activating influences are observed with most *ortho*-and-*para*-directing groups,¹ the effects being most marked for those at the left of the foregoing list, such as NH₂ and OH. These powerfully activating groups not only increase the ease of substitution of *o*- and *p*-hydrogen atoms in all the usual reactions of benzene but enable these atoms to enter into various reactions to which benzene itself is inert. Examples will be noted as they are encountered.

Conversely, all *meta*-directing groups exert a *deactivating* influence. This makes further substitutions more difficult in *all* positions, but hydrogen atoms in the *meta* positions are least deactivated, and it is here that substitution is most apt to occur—if and when it occurs at all. We have already noted (Sec. 5.10) the increased difficulty of nitrating nitrobenzene and pointed out the practical impossibility of introducing a third substituent into dinitrobenzene.

The more important *facts* concerning directing influences, activation, and deactivation in aromatic substitutions have just been summarized. The explanatory theory will be considered (Secs. 22.6ff) after the student has become acquainted with a greater variety of organic compounds.

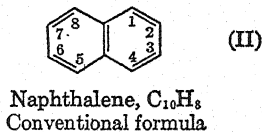
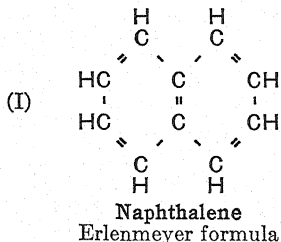
¹ Halogen atoms are exceptions to this rule; they are almost exclusively *o*-and-*p*-directing but retard the rate of further substitution (Sec. 22.9).

POLYNUCLEAR HYDROCARBONS

Compounds containing more than one aromatic nucleus are called *polynuclear*. The nuclei may be independent—that is, with no carbon atom in common—as in biphenyl (Sec. 23-3), or they may be *condensed* as in naphthalene, anthracene, phenanthrene, etc.

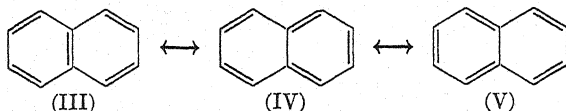
5-21 Naphthalene, $C_{10}H_8$, is obtained in large quantities from coal tar (Sec. 6-24). It is a colorless solid (m.p. $80.1^\circ C$; b.p. $217.9^\circ C$; d , 1.162) which crystallizes in shining plates and readily sublimes; its characteristic odor is familiar in “moth balls.” Naphthalene rather closely resembles benzene in most of its chemical properties but is, in general, somewhat more reactive. It is readily nitrated and sulfonated; chlorine and bromine substitute even without the aid of a catalyst. Hydrogen can be added by nickel catalysis and also by other, less active reducing agents. Naphthalene is not oxidized by cold permanganate or other mild oxidizing agents; vigorous oxidation converts it into phthalic anhydride (Sec. 24-10), its most important product. Naphthalene is used also for the manufacture of many substitution products which are intermediates in the dyestuffs industry.

5-22 Structure of Naphthalene. The chemical relations of naphthalene leave no doubt but that its 10 carbon atoms form two symmetrical six-carbon rings *with two carbon atoms participating in both rings*. It is this fused-ring structure which gives rise to the term *condensed nuclei*. Further, it is well established that the eight hydrogen atoms occupy the positions shown in the Erlenmeyer formula (I) and by the numbered angles in the conventional formula (II):



The Erlenmeyer formula has the same limitations as the original Kekulé formula for benzene, upon which it was based. Naphthalene is now regarded as a resonance hybrid, of which the three more important contributing forms¹ are represented (omitting the hydrogen atoms) as follows:

¹ Resonance energy increases with the number of forms which make appreciable contributions to the actual state of the molecule. Thus naphthalene is stabilized by 77 kcal per mole as compared with 39 to 41 kcal for benzene (both values are calculated from heats of combustion).

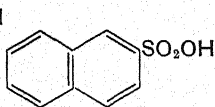
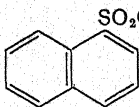


X-ray diffraction measurements indicate that all carbon-to-carbon bonds are equal in length; that is, there is no difference which would indicate alternate single and double bonds. But there is considerable evidence that in *chemical* reactions naphthalene usually acts as though the bonds were fixed in the positions shown in (III), which is the original Erlenmeyer formula.

For most purposes the conventional formula (II) is entirely adequate. In this symbol, each numbered position stands for a carbon atom *with one hydrogen atom attached*. The two angles that are not numbered represent the carbon atoms which are common to both rings; these carry no hydrogen.

5-23 Isomeric Substitution Products. Experiments show that two—but only two—isomers are possible when *one* hydrogen atom of naphthalene is replaced by some other atom or group. This fact can be accounted for if the naphthalene molecule is symmetrical and if a hydrogen atom occupies each of the numbered positions. On this assumption, positions 1,4,5, and 8 are identical; hence, only one compound should result, no matter which of these is entered by a substituting group. By convention, the formula of this compound is always written with the substituent in position 1; it is described by placing 1- or the Greek letter *alpha* (α) before the name. Turning now to positions 2,3,6, and 7, we see that these likewise are identical among themselves; replacement of any one of these hydrogen atoms gives the 2- or *beta* (β) substitution product. But *alpha* and *beta* monosubstitution products are different, and models representing them¹ cannot be turned in any way so that they may be superimposed, *e.g.*,

1-Naphthalene-
sulfonic acid
or
 α -Naphthalene-
sulfonic acid

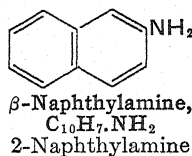
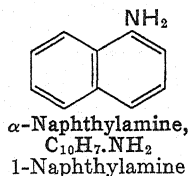


2-Naphthalene-
sulfonic acid
or
 β -Naphthalene-
sulfonic acid

Naphthyl Radicals. The univalent radicals corresponding to these two types of naphthalene monosubstitution products are known, respectively, as the α -naphthyl and the β -naphthyl radicals. These terms are often

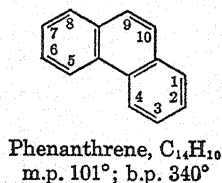
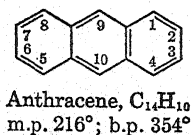
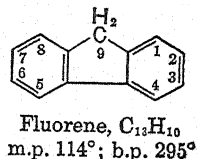
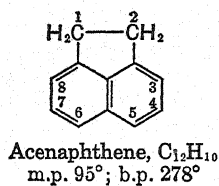
¹ The relations here considered are best understood by cutting from cardboard a number of pairs of (regular) hexagons with one side in common. Substitution in any position can be indicated by fastening on with a paper clip a piece of colored paper. Such models are particularly useful when considering isomerism among naphthalene disubstitution products.

used in naming simple derivatives of naphthalene, *e.g.*,



5-24 Substitution Reactions. Hydrogen atoms in the *alpha* positions of naphthalene can be substituted rather more readily than hydrogen in benzene. Thus, 1-chloronaphthalene and 1-bromonaphthalene are readily formed by direct substitution without the aid of a catalyst; 1-nitronaphthalene is manufactured by the use of relatively dilute nitric acid. The corresponding 2- or β -compounds are obtained by indirect methods. Sulfonation likewise takes place most readily in an α -position, but the results are more influenced by temperature (Sec. 14-3). Naphthalene substitution products are considered further in Section 24-6.

5-25 Higher Polynuclear Hydrocarbons. Many other hydrocarbons are known which contain aromatic nuclei condensed as in naphthalene. Four of those which are isolated in commercial quantities from coal tar are represented below by formulas which show correctly the relative positions of the carbon atoms and the hydrogen atoms—one hydrogen at each numbered angle. For each of them it is possible to write additional formulas with different but equally probable positions of the double bonds; all are regarded as resonance hybrids.



Anthraquinone (Sec. 24-13) can be made from anthracene by oxidation at positions 9 and 10. The phenanthrene nucleus occurs in many important natural products, including the steroids, abietic acid, and morphine.

5-26 Recognition of Aromatic Hydrocarbons. Pure specimens of most aromatic hydrocarbons are readily distinguished from alkenes, cyclenes, and other typically unsaturated compounds by their failure to add bromine and to reduce permanganate solutions. (Exceptions are styrene and a few other benzene derivatives with unsaturated side chains.) The most useful test for distinguishing from alkanes and cyclanes is treatment with cold fuming sulfuric acid containing 20 per cent sulfur trioxide; practically all aromatic hydrocarbons are sulfonated at room temperature, and the resulting sulfonic acids *dissolve* in the reagent.

5-27 Identification of Hydrocarbons. In the systematic procedure for identifying organic compounds a substance is classified as a hydrocarbon after its *failure* to respond to a series of tests for other classes of compounds. With few exceptions, it is not possible to convert aliphatic and alicyclic hydrocarbons into solid derivatives, and final identification usually has to depend upon close agreement in several *physical properties* (melting point, boiling point, index of refraction, density) with those of compounds described in the literature. Aromatic hydrocarbons on the other hand can usually be converted rather easily into solid derivatives with sharp melting points, which greatly facilitates their identification. The commonest methods are nitration (*e.g.*, benzene to *m*-dinitrobenzene, m.p. 89.8°C) and the oxidation of side chains (*e.g.*, isopropylbenzene to benzoic acid, m.p. 121.7°C). Some aromatic hydrocarbons, especially those of polynuclear structure, yield crystalline addition products with picric acid (so-called hydrocarbon picrates) which melt sharply and serve as useful derivatives.

Questions

1. Compare the *physical* properties of benzene with those of *n*-hexane, 1-hexene, and cyclohexane and suggest a reason for the relatively high melting points of benzene and cyclohexane (cf. Sec. 2-22).
2. Compare the *chemical* properties of benzene with those of the three hydrocarbons mentioned above.
3. Give specific chemical evidence for the presence of a six-carbon *ring* in benzene.
4. Give the reasons why, in your judgment, the special chemical properties of benzene cannot be due simply to the presence of: (a) the closed ring; (b) three ethylenic double bonds.
5. Explain accurately the difference between Kekulé's conception of the structure of benzene and the view that benzene is a resonance hybrid.
6. What significance attaches to the fact that the addition of one molecule of hydrogen to benzene is endothermic, while the additions of a second and a third molecule are exothermic?
7. Which of the following pairs of positions in benzene disubstitution products are *ortho*, *meta*, and *para*, respectively: 2,5; 4,6; 3,4; 3,6; 4,5?
8. Show how many isomers are possible of any benzene substitution product of the type: (a) $C_6H_5X_3$; (b) $C_6H_4X_4$; (c) C_6HX_5 .
9. Write structural equations for the reactions (in successive stages) of benzene with one, two, and three molecules of: (a) chlorine with iron; (b) nitric acid; (c) sulfuric acid.
10. Summarize your own laboratory observations which give physical evidence that new compounds are formed when benzene is treated with: (a) bromine and iron; (b) concentrated nitric acid; (c) fuming sulfuric acid.
11. Contrast the behavior of benzene toward the reagents mentioned in questions 9 and 10 with the responses to be expected of hexane, cyclohexane, and any hexene.

12. Write structural equations for two reactions of benzene in which the nuclear structure is destroyed.

13. (a) Describe the essential structure and give the general formula of the homologues of benzene. (b) Are styrene and naphthalene benzene homologues? Explain your answers.

14. Write structural equations for the preparation of ethylbenzene: (a) by the Wurtz-Fittig reaction; (b) by the Friedel-Crafts reaction. What organic by-products would be expected in these preparations?

15. What is the relation between benzyl chloride and *p*-chlorotoluene? Under what conditions can each be prepared from toluene? What would each yield on oxidation?

16. Write equations for the probable reactions of ethylbenzene with the following reagents: (a) cold fuming sulfuric acid; (b) hot concentrated nitric acid; (c) boiling potassium permanganate; (d) chlorine in sunlight (iron absent); (e) chlorine in the presence of iron; (f) ethyl bromide with anhydrous aluminum chloride; (g) hydrogen in the presence of hot finely divided nickel.

17. What is the objection to using concentrated (70 per cent) instead of 25 per cent nitric acid for the purpose of oxidizing toluene to benzoic acid?

18. Write the structural formula of a benzene homologue isomeric with the xylenes and explain how it would differ from any of the latter in the oxidation product.

19. A certain aromatic hydrocarbon is known to have the formula C_9H_{12} . Write a possible structural formula for it if, on oxidation, it yields an acid containing: (a) seven carbon atoms; (b) eight carbon atoms; (c) nine carbon atoms.

20. In an exhaustive examination, Körner established that a certain one of the xylenes gave *two* mononitro derivatives and that a third could not be obtained by any method, direct or indirect. Did this compound have the *ortho*, the *meta*, or the *para* structure? Prove your answer by suitable formulas.

21. The following mixtures were treated with anhydrous $AlCl_3$; write structural equations for any reactions that would be expected to occur and if none occurs explain why: (a) toluene and ethyl bromide; (b) toluene and bromobenzene; (c) *n*-hexane and ethyl bromide; (d) cyclohexane and benzyl chloride; (e) toluene and benzyl chloride.

22. Write the structural formulas of the major product or products to be expected if: (a) $C_6H_5.NH_2$ is mono and disulfonated; (b) $C_6H_5.COOH$ is mono and dinitrated; (c) $C_6H_5.C_2H_5$ is mono and dibrominated (in the presence of iron); (d) $C_6H_5.NO_2$ is reacted with CH_3Br and $AlCl_3$.

23. Which of the above reactions (in the mono stage) would proceed more readily than with benzene and which less readily?

24. Which of the following pairs of names refer to identical compounds: (a) 1-nitronaphthalene and 5-nitronaphthalene; (b) 4-naphthalenesulfonic acid and β -naphthalenesulfonic acid; (c) 8-nitronaphthalene and α -nitronaphthalene.

25. Write structural equations, indicating correct positions, for the reactions of naphthalene with one molecule of: (a) nitric acid; (b) bromine; (c) sulfuric acid (see Sec. 14.3).

26. Write other structures for anthracene and phenanthrene (see Sec. 5.25) which contribute to the actual state of these hybrid molecules.

27. A compound known to contain carbon and hydrogen *only* is under examination. What conclusion would you draw as to the class of hydrocarbons to which it belongs if *one* of the following observations were made: (a) It rapidly discharges the color of a solution of bromine in CCl_4 and reduces much permanganate solution? (b) It is unaffected by the above reagents and by cold sulfuric acid and only turns slightly brown when heated with that acid? (c) The compound is insoluble in and apparently

unaffected by cold sulfuric acid but dissolves in 20 per cent fuming sulfuric acid; when the resulting solution is diluted by pouring on to crushed ice, a white solid separates? (d) It dissolves in cold sulfuric acid and nothing separates when this solution is poured on to ice? (e) It reacts violently with cold sulfuric acid, giving off much heat, turning black, and remaining insoluble in water?

28. Summarize all the properties which are characteristic of *aromatic* hydrocarbons.

CHAPTER 6

PRODUCTS OF PETROLEUM AND COAL

Twentieth-century civilization depends to a very large extent upon carbonaceous residues of plant and animal life which were stored up in the crust of the earth during long past geological ages. This statement applies both to energy¹ and to innumerable material substances which have come to be regarded as necessities.

The annual world production of petroleum is of the order of 3.4 billion barrels, of which the United States produces about 54 per cent. This country also produces and delivers to consumers some 5,000,000 *million* cubic feet of natural gas and mines 600 million tons of coal. The great bulk of all these is used to generate heat and power by combustion. But chemical industry is using larger and larger amounts of raw materials, obtained cheaply and abundantly from these sources, for the manufacture of other organic compounds which are more useful and, therefore, more valuable.

NATURAL GAS AND PETROLEUM

6.1 **Natural gas** always accompanies petroleum and, by reason of its greater freedom of migration within the earth, is also obtained from *dry* wells that yield no oil. Its composition varies considerably in different localities. In the United States the combustible components—on which its fuel value depends—are almost entirely the lower alkanes; for the country as a whole, it has been estimated that about 85 per cent is methane, 9 per cent ethane, 3 per cent propane, 1 per cent butane, and the remainder pentanes, hexanes, etc. Nitrogen is the most abundant non-combustible component. Some specimens of high nitrogen content also contain 1 to 2 per cent of helium; these serve as the only industrial source of that gas.

Natural gas is used chiefly as an industrial and domestic fuel, but large quantities are consumed in the manufacture of carbon black and for the other purposes described in Section 6-13. It is also the source of the following products.

Natural Gasoline. It is a familiar fact that air which has been in contact with water becomes more or less saturated with water vapor. In

¹ Natural gas and petroleum furnished about 56 per cent of the energy produced in the United States in 1950, coal about 39 per cent, and water power the remainder.

exactly the same way, natural gas which has been in contact with an underground pool of petroleum carries vapors of the lower boiling liquids contained in the oil. When separated from the true gases, these vapors condense to a mixture of volatile, liquid hydrocarbons known as *natural gasoline*. This consists mainly of hexanes and heptanes with some pentanes and octanes. Most of the natural gas distributed to consumers through pipe lines in the United States is first stripped¹ of natural gasoline, with an average yield of about 1 gallon per 1000 cubic feet of gas. Natural gasoline is blended with petroleum distillates to increase the proportion of low-boiling components in finished motor fuel and accounts for about one-tenth of the total volume sold.

Liquefied Petroleum Gases. Crude natural gasoline as first isolated contains dissolved propane and butanes which must be removed before it is incorporated into motor fuel. Considerable amounts of these gases are liquefied under pressure and shipped in steel cylinders as *liquefied petroleum gases* (LPG), or "bottled" gas. This is widely used for domestic and industrial heating in areas not accessible to natural-gas pipe lines.

6-2 Petroleum is an oily liquid varying in color from amber to black; it is lighter than water, in which it is practically insoluble. Petroleum is an extremely complex mixture consisting mainly of hydrocarbons with much smaller amounts of organic compounds of sulfur, nitrogen, and oxygen. The hydrocarbons are largely alkanes and naphthenes;² aromatic hydrocarbons are usually present but rarely in excess of 0.5 to 2 per cent. Crude petroleum is classified as *asphalt* base, *paraffin* base, or *mixed* base, depending on the proportions of asphalt and of paraffin wax contained in the highest boiling distillates or distillation residues.

Some of the hydrocarbons in crude petroleum are dissolved *gases*—methane to butane—retained in solution from the natural gas with which the oil was in contact within the earth. Much the larger portion is a mixture of *liquid* hydrocarbons of low, medium, and high boiling points and with widely varying viscosities. The remainder consists of *solids* or *semisolids* such as the compounds that make up paraffin wax and asphalt. The properties of such a mixture are not such as to make it particularly useful for any purpose; hence, substantially all petroleum produced is *refined* to more useful products.

¹ Some of the "gasoline" in natural gas can be removed by compressing and chilling—just as water is condensed from moist air by similar treatments. Further amounts are recovered by absorption in a spray of cold, high-boiling oil, or by adsorption on the surface of a finely divided solid such as activated charcoal or silica gel.

² In the petroleum industry the term *naphthene* is used to describe all the saturated cyclic hydrocarbons. These include the cyclanes (Sec. 4-3) and more complex substances containing fused rings.

6-3 Straight-run Refining. The fundamental operation in refining petroleum is some method of fractional distillation. In modern refineries this is a continuous process, conducted in pipe stills. The essentials of such an installation are: (1) a *bank of continuous piping*, several hundred feet in length, set in a firebox; here the current of oil passing through is brought to a temperature of about 400°C; (2) an *evaporator*, a large insulated vessel to which no external heat is applied; when the hot oil enters the evaporator, all its components volatile up to 400°C boil off, leaving a residue of fuel oil which settles and is periodically withdrawn from the bottom; (3) an efficient *condensing system* to receive the vapors from the evaporator. In the towers composing the latter system, *fractional condensation* occurs; the higher boiling components condense first and are withdrawn at the proper point as gas oil; on further cooling, kerosene condenses and then crude gasoline. The uncondensed permanent gases—methane to butane—furnish fuel for the firebox. Heat is conserved by using crude oil as the cooling agent to reduce progressively the temperature in the condensing system; in this way the crude is heated to about 150°C before it enters the still.

The boiling ranges of the crude condensates are approximately as follows:

Crude gasoline (benzine).....	Up to 220°C
Crude kerosene.....	220 to 300°C
Gas oil.....	300 to 400°C

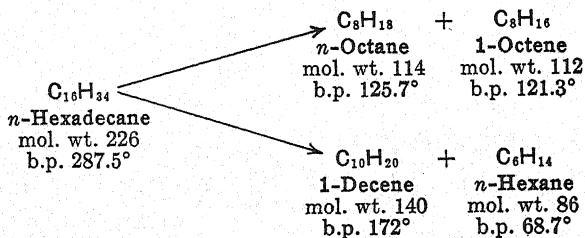
Each of these fractions is further treated according to its nature and intended uses. Most distillates are agitated at least once with sulfuric acid and, if they contain much sulfur, with a solution of sodium plumbite. After thorough agitation with water to remove such added chemicals, each product is redistilled with a fractionating column to limit its boiling range.

A portion of every crude—ranging 20 to 80 per cent of the original volume—does not vaporize at 400°C and drops to the bottom of the “evaporator,” from which it is periodically withdrawn. Depending on the nature of the crude, such distillation residues may be: used for the manufacture of *lubricants* and/or road tars and asphalt; sent to cracking stills; or burned like coal as a fuel for raising steam, *i.e.*, as *fuel oil*.

The general procedure just outlined—which may be varied in many details—is usually described as *straight-run* refining. The separation processes are strictly physical and, in so far as chemicals are used, it is for the purpose of removing impurities; the hydrocarbons that make up the great bulk of petroleum and its distillates undergo no change. In other words, the molecules that compose the various products are molecules that were *present as such* in the original crude as it came from the ground.

Thus it follows that the yield of the most valuable product, gasoline, obtainable by straight-run refining is limited to the volume of low- and medium-boiling (40 to 200°C) liquids present in the crude. This varies widely for different crudes but averages about 8.5 gallons per barrel of oil. To put it another way, 5 barrels of average crude petroleum is required to produce 1 barrel of gasoline by straight-run refining.

6.4 Cracking is a *chemical* process through which the yield of gasoline per barrel of crude has been greatly increased. All the earlier industrial methods depended primarily on the effects of heat (*thermal cracking*). With rising temperatures, the kinetic energy of molecules increases. They move faster, strike harder, and are subject to more intense internal vibrations. Above some minimum temperature—characteristic for any given compound—these effects of higher kinetic energy break chemical bonds and the molecule splits into simpler parts. Thus, when strongly heated, the large molecules of high-boiling petroleum distillates may split into simpler ones boiling within the gasoline range (40 to 200°C). This would be the result if, for example, *n*-hexadecane should “crack” in either of the following ways:



This, the fundamental principle of thermal cracking, has long been known. It is quite another matter to apply it in such wise as to obtain high yields of gasoline hydrocarbons. All cracking stocks¹ are highly complex mixtures, and any individual hydrocarbon chain may cleave in different places. At effective cracking temperatures (400 to 600°C), dehydrogenations occur, together with various side reactions leading to the formation of coke and high-boiling tars. The effective control of thermal cracking processes to obtain good yields of products boiling in the gasoline range depends largely on the length of time in the cracking zone and the temperatures used. These temperatures are always above the boiling points of the cracking stock, thus requiring that the operations be conducted under considerable pressures—up to 1000 psi (pounds per

¹ *Cracking stocks* may be almost any high-boiling petroleum distillate or distillation residue. In many refineries the crude oil is *topped*—i.e., the native gasoline hydrocarbons are removed in a special stripping still—and the entire remainder, which may amount to 80 to 90 per cent of the crude, is passed to the cracking stills.

square inch) in some methods. Many thousands of patents cover the design and operation of cracking processes, of which many have been used industrially and then superseded.

6.5 Catalytic Cracking. The manufacture of gasoline was revolutionized during the decade 1940–1950 by the widespread introduction of catalytic cracking units ("cat crackers"). A number of these are in extensive use—*e.g.*, Houdry, Fluid catalyst, Thermoform, Cycloversion. Details are beyond the scope of this book, and it must suffice to emphasize that catalytic methods have achieved their popularity because: they operate at lower temperatures (*e.g.*, 250 to 275°C) and thus afford better control over the products; most of them operate at atmospheric pressure, thus eliminating the need for high-pressure equipment; they yield crude gasolines of higher octane numbers (Sec. 6.6) than those from thermal cracking; and they yield less methane and more of the three- and four-carbon gases.

Cracking-still Gases. Large amounts of gases are produced in any cracking process. These include hydrogen and various gaseous hydrocarbons, formed when cracking occurs near the end of a larger molecule and a one- to four-carbon fragment is split off. Formerly, when the sole objective was to produce low-boiling *liquids* for gasoline, all such gases were waste products and were usually burned as fuel under the cracking stills. This situation has been altered sharply by the present demand for some of these gases as raw materials for chemical syntheses, such as the production of 100-octane motor fuel and synthetic rubber described later in this chapter. The gaseous hydrocarbons now produced in enormous quantities as by-products of cracking consist, principally, of the following:

<i>Alkanes</i>	<i>Alkenes</i>
Methane	Ethylene
Ethane	Propene (propylene)
Propane	1-Butene } (butylenes)
<i>n</i> -Butane	2-Butene }
Isobutane	Isobutene (isobutylene)

6.6 Gasoline. The major product of the petroleum industry, both in volume and in value, is fuel for internal-combustion engines of the kind used in automobiles and airplanes. This is called gasoline in the United States and *petrol* in many other countries. Since it is a mixture, the composition of gasoline can be varied at will by refinery practices. Actually, its composition is governed by the need to furnish a product that will please the consumer. Aside from the absence of gum-forming and corrosive agents, the chief requirements of a motor fuel are adequate volatility and the ability to develop power in an internal-combustion engine.

Volatility. A motor fuel must contain enough easily volatile hydrocarbons to permit easy starting and must not contain an excessive amount of high-boiling compounds. This requirement is met by limiting the composition to hydrocarbons boiling between approximately 40 and 200°C, mixed in such proportions as to give a smooth distillation curve. As already stated, the chief use of natural gasoline is for blending with refinery distillates to increase their content of easily volatile hydrocarbons.

Power. Other things being equal, we should get the most power from that fuel which, on burning, yields the greatest number of calories per gallon. In practice, however, the per-gallon mileage of a car and the speed and maneuverability of an airplane depend much less upon the total potential energy of the fuel than on the efficiency of the engine in converting this into power. Greater efficiency is attained in engines where the mixture of fuel and air is highly compressed before ignition. In such *high-compression* engines straight-run gasoline tends to explode before the piston head reaches the end of its stroke, and this premature explosion causes engine knock and loss of power. This has led to the development and large-scale production of antiknock or *high-octane* motor fuels, which are highly desirable in automobiles and indispensable in aviation.

Octane Ratings. The antiknock quality of a motor fuel can be measured by comparing its behavior in an engine of specified design and mode of operation with that of standard samples under identical conditions. The fundamental standards are mixtures in known proportions of normal heptane (knock producing) and the highly branched octane, 2,2,4-trimethylpentane, commonly called *isooctane*.¹ The latter has excellent antiknock qualities and is arbitrarily assigned the octane number 100. *The octane number of a motor fuel is the percentage of isooctane contained in the standard which the specimen matches in performance.* For example, to say that a certain gasoline has an octane number of 75 means that its engine performance is equal to that of a mixture of 75 parts isooctane and 25 parts normal heptane.

The octane ratings of motor fuels can be raised by adding small amounts of certain compounds which are not hydrocarbons. By far the most effective of these is *tetraethyllead*, $(C_2H_5)_4Pb$, commonly referred to in the industry as TEL. This is used in substantially all gasoline sold at the present time, being added² at the rate of 1 to 3 ml per gallon. The

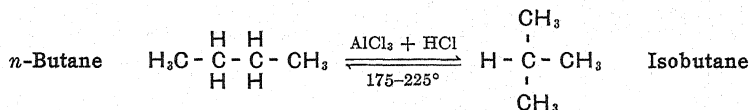
¹ Following universal practice in the petroleum industry, the word isooctane will be used hereafter as referring to 2,2,4-trimethylpentane.

² Tetraethyllead, a toxic substance, is added in the form of so-called *ethyl fluid*—which also contains a coloring matter, usually red, to warn of its presence, and ethylene dibromide, $C_2H_4Br_2$. The latter is included so that, on combustion, the lead will be converted into volatile lead bromide which escapes through the exhaust; without it, nonvolatile lead oxide would accumulate in the engine.

increase in octane rating produced by adding 1 ml of TEL per gallon is called the *lead susceptibility* of the fuel. This is greatly reduced by the presence of compounds containing sulfur, for which reason much care is taken to remove all but traces of sulfur in gasoline refining.

6.7 Chemical Structure and Octane Rating. Experiments have shown that motor performance is greatly affected by the structure of the molecules composing the fuel. The normal alkanes tend to burn explosively and produce engine knock most readily; branched-chain alkanes, aromatic hydrocarbons, and alkenes burn much more smoothly under high compression. With few exceptions, *straight-run* gasolines (consisting largely of normal alkanes and cyclanes) have octane ratings so low that addition of TEL does not improve them sufficiently. This situation had led to many technical advances in gasoline manufacture, all designed to increase the content of knock-retarding hydrocarbons. There are two approaches, fundamentally different. One of these is to improve the quality of gasolines obtained by standard methods, *e.g.*, by isomerization or aromatization; the other is the synthesis of high-octane gasolines from hydrocarbon gases.

6.8 Isomerization. In the presence of certain acid catalysts (such as $\text{AlCl}_3 + \text{HCl}$ and $\text{BF}_3 + \text{HF}$) normal alkanes are converted more or less extensively into their branched-chain isomers. Any such change is called an *isomerization*. An important and typical example is the manufacture of isobutane from the much more abundant *n*-butane:



Such changes are always reversible, and there results an equilibrium mixture which varies in composition with the temperature. As conducted industrially, about 40 to 45 per cent of the *n*-butane charged is converted to isobutane in the first pass over the catalyst; the iso compound is then separated and the unchanged *n*-butane recycled.

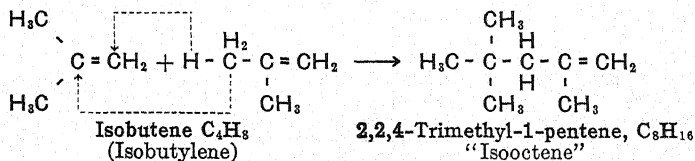
Similar isomerizations of higher alkanes¹ occur during *catalytic cracking*, thus contributing to the higher octane ratings of the crude gasolines produced in this way. Special aftertreatments—which may be either thermal or catalytic—are applied also to gasolines of low octane numbers obtained from any source, to increase their content of isoalkanes. In the petroleum industry this is known as *reforming*.

¹ It is interesting, though technically unimportant, that even propane is isomerized by heating over suitable catalysts. This was shown by using a synthetic propane in which one of the end carbons was the heavy isotope, C^{13} . After treatment, the heavy carbon atom was found in the middle of the molecule.

6-9 Aromatization. Aromatic hydrocarbons have high octane ratings and are therefore desirable components of motor fuel. Any procedure which brings about their formation from hydrocarbons of other types is described in the petroleum industry as *aromatization*. This always occurs to some extent under the conditions which promote cracking and isomerizations, but several special methods have been devised with this specific objective (*e.g.*, the *hydroforming* and *cycloversion* processes). It is said that one of these can convert a 40- to 45-octane base stock into 80-octane gasoline with an 80 per cent yield and that the resulting gasoline contains 40 to 50 per cent of mixed aromatic hydrocarbons. The chemistry of aromatization is described in more detail in Section 6-18.

6-10 Synthetic Gasolines. The demand for "100-octane gasoline" for aviation during the Second World War led to the large-scale development of two processes in which highly branched alkanes in the gasoline boiling range are synthesized from hydrocarbon *gases*. These methods are polymerization and alkylation.

Polymerization. One way to obtain isooctane is through the dimerization of isobutene. This can be effected by passing the gas at a moderate temperature (*e.g.*, 150°C) over a catalyst such as solid phosphoric acid. The over-all reaction may be pictured as follows:

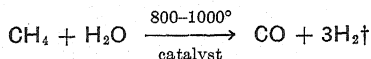


(Reaction probably occurs through the carbonium-ion mechanism described in Section 3-12. Various isomers are also formed through side reactions which cannot be discussed here.) The product is saturated, producing isooctane, by hydrogenation over nickel. Similarly, mixtures of butene and isobutene and of propene and isobutene are copolymerized (Sec. 6-16) to highly branched octenes and heptenes, respectively, which are subsequently hydrogenated.

Alkylation Process. This method has the advantages of not requiring the final hydrogenation step and being more economical in the use of isobutene. The over-all reaction is the addition of an isoalkane to an alkene (ethylene, propene, a butene, or isobutene). The isoalkane must be one containing a hydrogen atom attached to a *tertiary* carbon; practically, this means that *isobutane* is the only suitable gas available. Reaction occurs at room temperature or below in the presence of catalysts such as H_2SO_4 or anhydrous HF . A typical example of the over-all result¹ is

¹ A rather complicated carbonium-ion mechanism is probably involved.

Another method is the so-called methane-steam reaction:



The Fischer-Tropsch process originated in Germany where the necessary gas mixture was obtained by the action of steam on hot coke—the *water-gas* reaction ($\text{C} + \text{H}_2\text{O} \longrightarrow \text{CO} + \text{H}_2$). It has been operated there to manufacture liquid fuels from coal.

6-12 Other Petroleum Products. In addition to gasoline, petroleum refining yields important quantities of other industrial products which can only be mentioned here. Broadly speaking, each of these is still a complex mixture; the refining methods are primarily physical and seek only to limit the composition of each to compounds which are similar with respect to some useful property. Various mixtures of hydrocarbons distilling in the lower part of the gasoline range are separated in the volumes which their use demands and sold, under such names as *naphtha*, *petroleum ether*, and *ligroin*, as industrial solvents; these are used in extracting fats and oils, in dry cleaning, etc. Others, arranged roughly in the order of decreasing volatility, include: kerosene, for oil lamps and stoves; gas oil, which is a favored cracking stock and also a source of diesel fuel; lubricating oils and greases of many different grades¹; paraffin wax; road oils; petroleum asphalt, for paving and roofing; and fuel oil. The latter is any petroleum product used as a substitute for coal to generate heat by combustion in a firebox; it may be gas oil (a *distillate*), but more commonly it is a *distillation residue* unsuited for any other purpose.

CHEMICAL PRODUCTS FROM NATURAL GAS AND PETROLEUM

In the methods described above, hydrocarbon gases are used for the production of *mixtures* which are suitable for use as liquid fuels. We turn now to consider natural gas and petroleum as sources of raw materials for the chemical industry. For this latter purpose, it is usually necessary to isolate *individual compounds* in a relatively pure state.

† If desired, this gas may be mixed with more steam and passed over another catalyst to give



Since the carbon dioxide is easily removed by scrubbing with water, this has become an important source of industrial hydrogen.

¹ The usual production of 50 million barrels of lubricants—for motor vehicles, aviation, and industrial plants—is a major and highly specialized part of petroleum refining and one which is indispensable in the machine age. The processes are largely physical and cannot be discussed here.

6-13 Products of Methane. The high stability and low reactivity of methane have made it so far the least useful of the hydrocarbon gases as a chemical raw material—although it is the most abundant. The Fischer-Tropsch process holds out promise, but there remains the problem of separating individual compounds from the complex mixtures which it yields. Water gas, produced from coke or from natural gas, is also used in the large-scale synthesis of methanol (Sec. 8-15) and in the Oxo process for making aldehydes from alkenes (Sec. 10-3, paragraph 2). The production of *acetylene* from natural gas is beginning (1951) to become commercial. This involves exposing methane to a high temperature, 1300 to 1500°C, for a very short time; in one method methane is passed through an electric discharge; in another, the required temperature is obtained by burning part of the methane with oxygen. Another high-temperature reaction of growing importance is with ammonia to give hydrogen cyanide ($\text{CH}_4 + \text{NH}_3 \longrightarrow \text{HCN} + 3\text{H}_2$). Chlorination of methane to methyl chloride and methylene chloride has been mentioned (Sec. 2-4).

Carbon black is very finely divided carbon. It is produced from surplus natural gas by several different thermal methods, each of which yields particles of different sizes and somewhat different physical properties. Most methods depend upon combustion in a *limited* supply of air. This is utilizing on a large scale an observation which every laboratory worker has made when the air supply of a Bunsen burner is reduced too much; the flame becomes yellow and luminous, due to particles of incandescent carbon, and a cold dish placed in it is quickly blackened by a soft film of carbon. Another method depends on the thermal decomposition¹ of methane at temperatures above 1000°C. All the methods are quite inefficient and yield only a small percentage of the total carbon of the gas consumed.

The annual production of carbon black in the United States is about 1.2 billion pounds. Much the largest part of it is used in rubber compounding, especially for tires where it is indispensable. This is also the principal "black" for printing inks and paints.

6-14 Alkene Addition Products. The most important sources of pure chemical compounds and other synthetic products from petroleum and natural gas are the unsaturated gases: ethylene, propene, the butenes, isobutene, and butadiene. These are available in large quantities in the gases from cracking stills (especially catalytic cracking), and additional amounts are produced cheaply from the even more abundant alkanes of natural gas by cracking or dehydrogenation.

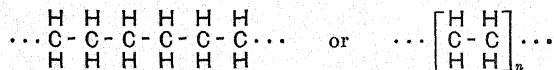
¹ A special procedure is necessary. If decomposition is brought about by contact with a heated solid, such as the wall of a glass or metal tube, carbon is deposited as a hard compact mass which has little use or value.

The usefulness of the alkenes for chemical syntheses depends upon the readiness with which they enter into various addition reactions. Some of these reactions have been outlined (Chap. 3), and others will be described later. Any attempt at this point to summarize all the compounds produced from them would be confusing. But, to give some idea of the importance of these gases as raw materials for industrial chemical syntheses, it may be mentioned that each of the following is manufactured in the United States from ethylene and propene in quantities of the order of 500 million pounds or more per year: ethyl alcohol, ethylene glycol, isopropyl alcohol, and acetone.

The major uses of the hydrocarbon gases containing four carbon atoms are for the manufacture of high-octane motor fuel (Sec. 6·10) and synthetic rubber. The latter involves the formation of high polymers.

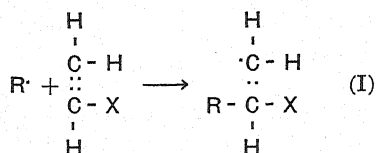
6·15 High Polymers. Polymerization has been described (Sec. 3·12) as a type of reaction which is capable in theory of repeating itself indefinitely. Actually, under appropriate conditions, thousands of certain unsaturated molecules combine with each other to form so-called high polymers. The products are mixtures of long, stringlike molecules of high molecular weight, in which some relatively simple structural unit is repeated again and again. Polyethylene is the simplest example.

Ethylene, liquified under pressures of 500 to 1200 atmospheres and heated to 150 to 250°C with a very small amount of oxygen, gives products of the composition $(C_2H_4)_n$. The average *degree of polymerization*, DP, which is the average value of n , depends upon the temperature, the pressure, and the amount of oxygen used. Different commercial products are said to vary in average molecular weight from 3000 to 50,000 (28,000 corresponds to DP 1000). Polythene is a trade name for polyethylene manufactured in the United States. It is a very tough substance which has excellent qualities as an electrical insulator and is rapidly finding many other applications, *e.g.*, in flexible bottles. The essential structure of its molecules can be represented by formulas such as

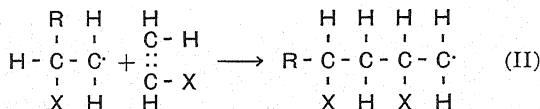


The significance of the end valences is explained below.

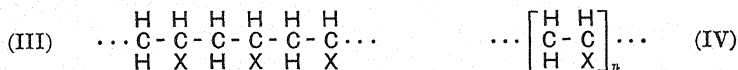
6·16 Mechanism of Polymerization. Many different compounds containing the grouping $C=CH_2$ are capable of forming high polymers by addition. Peroxides, such as benzoyl peroxide, are the catalysts most commonly used. These are believed to initiate polymerization by liberating organic free radicals. In the next step, a free radical (R') attacks a monomer molecule, adding to one side of the double bond and forming a product which is also a free radical:



This radical (I) attacks a second molecule of the monomer, again transferring the odd electron:



Continuation leads to very long molecules with the general pattern¹ of (III), containing the repeating unit (IV):



Some of these reactions have been shown to proceed with enormous speed, a thousand or more monomer molecules uniting—apparently through this step-by-step process—in a small fraction of a second. In the manufacture of industrial high polymers it is necessary to use some means to interrupt the reaction when the desired average degree of polymerization has been reached.

Polymerization by peroxide catalysis² is thus seen as a *chain reaction* which continues as long as each intermediate is a free radical. A particular chain is broken—that is, its growth ceases—when a product loses its free-radical character. This probably occurs most frequently through the addition of some end group, E, in such fashion as to pair all electrons. It appears, therefore, that the true composition of a high polymer is indicated more accurately by (V) than by (IV):

¹ What we have implied here is a regular series of “head” to “tail” additions. This seems to be the general rule in the formation of high polymers but does not exclude the possibility of some “head-to-head” or “tail-to-tail” additions, leading to irregularities in the chain. X may be hydrogen or another atom or group.

² If a peroxide-catalyzed polymerization is interrupted before it runs its course, the mixture contains only unchanged monomer and high polymers; dimers and trimers cannot be detected. And, once reaction has been stopped, it is not usually possible to start it again. On the other hand, when dimers and trimers have been formed in other ways (*e.g.*, by acid catalysis, Sec. 3-12), they can be converted into the same high polymers which would have been obtained from the original monomer. Facts such as these are part of the evidence for the free-radical mechanism assumed for peroxide catalysis. Other agents known to be capable of producing free radicals, *e.g.*, tetraethyllead and short-wave radiation, act like peroxides in promoting addition polymerization.



But these polymers usually have molecular weights high in the thousands; the percentage represented by the groups indicated as R and E is so low as to make their presence extremely difficult, or impossible, to detect—and so low that they have no appreciable effects on the properties of the polymer. For these reasons high polymers are usually represented by formulas analogous to (IV), with no attempt to show how the indicated free valences at the ends of the chains are actually satisfied.

Copolymers. It is a common industrial practice to mix two unsaturated compounds and polymerize. With many pairs of compounds (though not all) molecules are formed which contain structural units from both monomers. The most important of these copolymers are the synthetic rubbers.

6.17 Synthetic Rubber. Natural rubber (Sec. 4.14) is a high polymer of isoprene. Strictly speaking, no one of the substances called “synthetic” rubber deserves that term since none of them is identical with the natural compound in composition and structure. All of them are, however, high polymers of *similar* structures and—what is more important—they can be vulcanized and then have the elasticity and other properties which give rubber its manifold uses. They are sometimes described as *elastomers*.

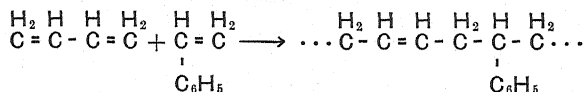
The synthetic rubber produced in much the largest amount is a copolymer of butadiene and styrene in the ratio of about 72 to 28 parts by weight. It is called GR-S in the United States and Buna S in Germany. The required butadiene is obtained in part by dehydrogenation of the butenes from cracking units and in part by the two-stage dehydrogenation of butane.¹ Styrene is manufactured by the dehydrogenation of ethylbenzene (Sec. 23.4). In the standard method of copolymerization, the metered hydrocarbons are stirred vigorously with a soap solution and some added chemicals² in a pressure reactor at 50°C until the desired average degree of polymerization has been reached. The polymer is obtained as a milky emulsion similar to native latex, which is coagulated, washed, and converted into sheet rubber by conventional methods. An

¹ When the demand requires it, butadiene is manufactured also from ethyl alcohol, a more expensive raw material. One method consists in dehydrogenation of alcohol to acetaldehyde, followed by a catalytic condensation reaction between acetaldehyde and excess ethyl alcohol.

² These include potassium persulfate, $K_2S_2O_8$, which acts with the soap to catalyze the reaction. Another substance added initially, in small amount, is a so-called “modifier,” such as dodecyl mercaptan; this controls the quality of the copolymer by terminating some molecular chains and starting others. After several hours a “short-stop,” such as hydroquinone, is added to destroy the persulfate and stop all further action.

important postwar development is a process for low-temperature polymerization (at around 0°C). The Ultipara rubber thus produced appears to be superior in a number of ways to the standard GR-S.

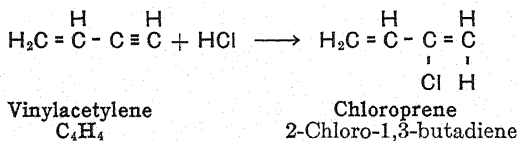
GR-S contains butadiene and styrene units in the molecular ratio of about 6:1, the union between them being of the type



But it appears that the spacing of styrene units is not uniform, and there may be 1 to 12 butadiene units between them. It may be noted also that while natural rubber is strictly a 1,4-addition polymer of isoprene, butadiene reacts both by 1,4- and 1,2-additions in copolymerizing with styrene.

Several other synthetic rubbers are produced in smaller but significant quantities, mainly on account of properties which make them superior to GR-S for special purposes other than the manufacture of tires. GR-N, a copolymer of butadiene and acrylonitrile, is especially resistant to the action of gasoline, oils, and chemical solvents (all of which are destructive to natural rubber and GR-S). It is sold under several trade names such as Hycar, Chemigum, and Perbunan. GR-I, or *butyl* rubber, is a copolymer of isobutene¹ and a small amount of isoprene. It has become the favorite material for making inner tubes because of its low permeability to air.

Neoprene (GR-M type), the first synthetic rubber produced successfully in the United States, is a product of acetylene. This gas is dimerized to vinylacetylene by passing it through a solution of cuprous and ammonium chlorides at room temperature. Vinylacetylene is then converted to chloroprene by passing through another solution of cuprous and ammonium chlorides, this time in concentrated hydrochloric acid:



Polymerization of chloroprene yields the vulcanizable high polymer *neoprene*, or GR-M, which has high resistance to heat and to the action of gasoline, oils, etc.

¹ The dimerization of isobutene to isooctene is represented by the first equation in Section 6-10. Isobutene also forms a high polymer, in which the same structure is continued. This polymer is *saturated* (with the possible exception of one double bond) and therefore cannot be vulcanized. Copolymerization with a little isoprene supplies the unsaturation necessary for successful vulcanization.

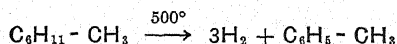
TABLE 6-1 PRODUCTION OF ELASTOMERS; USA, 1950

	Pounds
GR-S type (butadiene-styrene polymers).....	802,000,000
GR-M type (neoprene).....	112,000,000
GR-I type (butyl).....	125,000,000
GR-N type (butadiene-acrylonitrile).....	27,000,000
Polyvinyl type (Sec. 15-6).....	84,000,000
Others (thiokol, silicone, etc.).....	16,000,000
Total.....	1,166,000,000

Note. The total production of elastomers rose to just over 2 billion pounds in 1951. The major part of the increase was from the emergency operation of government plants which almost doubled their 1950 output of GR-S.

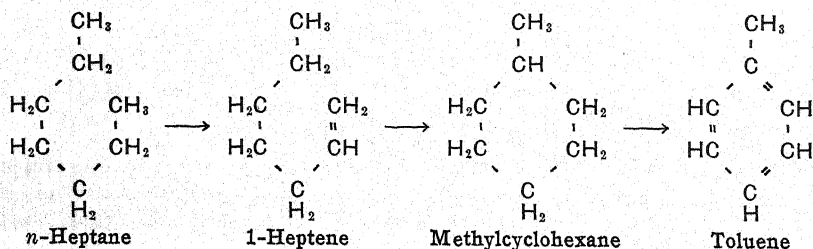
6-18 Aromatic Hydrocarbons from Petroleum. Prior to the Second World War, the petroleum industry in the United States was using several processes for improving the antiknock quality of gasolines by converting other components of petroleum into aromatic hydrocarbons (Sec. 6-9). No attempt was made to isolate individual compounds. The war demand for toluene, for making the high explosive TNT, led to modifications of these processes which now make petroleum the major source of toluene and the xylenes and a benzene source of growing importance.

The raw materials are selected petroleum distillates rich in certain cyclanes and alkanes. In so far as methylcyclohexane is present, only a catalytic dehydrogenation is necessary to yield toluene:



This is effected successfully by passing the vapors of methylcyclohexane mixed with hydrogen, at a total pressure of about 15 atmospheres, over a selected catalyst. (The reaction is truly a dehydrogenation although it is conducted in the presence of added hydrogen; this is used to regulate the reaction and to saturate by-products which interfere.) Under the same conditions, ethylcyclopentane and dimethylcyclopentane are isomerized to methylcyclohexane and then dehydrogenated.

Aromatics are also formed from aliphatic hydrocarbons by ring closure (cyclization) and dehydrogenation (aromatization) in the same operation. Illustrating with *n*-heptane, the sequence of changes is probably as follows:



Octane, methylheptanes, and dimethylhexanes in the charging stock yield a large amount of mixed xylenes as a co-product in the manufacture of toluene.

The production of aromatic hydrocarbons from petroleum shown in Table 6-2 is especially interesting in view of the fact that prior to about 1943 *none* came from this source. As the result of a current demand for more benzene than is available, several new plants brought its production from petroleum up to 234 million pounds in 1951.

TABLE 6-2 PRODUCTION OF AROMATIC HYDROCARBONS; USA, 1950
(In pounds)

	From petroleum	From coal	Total
Benzene.....	73,000,000	1,168,000,000	1,341,000,000
Toluene.....	328,000,000	276,000,000	604,000,000
Xylenes.....	450,000,000	68,000,000	518,000,000

6-19 Products of Controlled Oxidations. The combustion of even simple molecules like CH_4 and C_2H_6 to CO_2 and H_2O does not take place in one reaction (as is implied by our over-all equations) but proceeds step-wise, with the formation of various partially oxidized molecules. At the temperatures produced in ordinary burning, these intermediate products are further oxidized too fast to be isolated or, usually, to be detected. The results may be quite different, however, if hydrocarbon gases mixed with air in suitable proportions are heated to temperatures which can be *controlled*. This principle has recently (1949) been put into practical use on a large scale in Texas, using mixtures of propane and butane as the raw material. Regulated air oxidation yields a rather complex mixture of oxidation products containing one to four carbon atoms, from which a number of pure compounds are being isolated in commercial quantities. (The difficulty in separation is considerable but apparently not so great as with the by-products of the Fischer-Tropsch synthesis.) These compounds include methanol, formaldehyde, and acetic acid, all of which are themselves starting materials for many other organic chemicals.

Controlled oxidations are also applied to pure *alkenes* to obtain specific products; examples include the direct oxidation of ethylene to ethylene oxide and of propene to acrolein.

PRODUCTS OF COAL

6-20 The Carbonization of Coal. When bituminous coal is strongly heated in the absence of air, the complex organic compounds that make up the coal substances are decomposed into carbon and a mixture of vola-

tile products. This operation is known as the *carbonization of coal*. Certain varieties of bituminous coal, when heated to the necessary temperature, leave at the end a porous but hard residue of *coke*. When, as is usually the case, carbonization is conducted with the object of producing metallurgical coke, the operation is called *coking*. The volatile by-products of this operation are a major source of aromatic hydrocarbons.

Knowledge of the chemical reactions involved in carbonization is limited. Thermal decomposition or cracking of the complex organic molecules of the coal substance is certainly the first step. Following this, some of the simpler decomposition products are probably condensed or polymerized to yield the products actually obtained. It is certain that raw coal contains neither coal gas, coal tar, benzene, naphthalene, nor other simple aromatic hydrocarbons; *these are formed during the process of carbonization*.

6-21 By-product Coking. Metallurgical coke is now manufactured almost exclusively in *by-product ovens* designed for the recovery of the volatile substances formed during carbonization. The average oven is a narrow chamber, 14 to 18 inches wide, 28 to 40 feet long, and 10 to 14 feet high, holding about 12 tons of coal. These ovens are constructed of firebrick in batteries of 5 to 90 units, with flues built between in which burning gases provide the necessary heat. Each oven is provided with an *uptake pipe* leading to a common collecting main for the volatile products. Coal for coking is selected on the basis of its ash content and predetermined coking qualities. After washing and crushing it is charged into the ovens through openings in the tops, which are then sealed. At the end of the coking period (11 to 18 hours), the temperature in the middle of the oven is about 950°C and all volatile products have been driven off. Doors at each end of the oven are then opened, and the coke is discharged by a ram.

Coke is a hard gray porous mass consisting essentially of carbon, but containing also the mineral matter (ash) of the coal. Its largest use (about 70 per cent of the production) is in blast furnaces for the smelting of iron. For this reason the demands of the steel industry determine very largely the amount of coal carbonized. Normally, in the United States, this is about one-seventh of the soft coal mined.

Coke is used also for the manufacture of calcium carbide (route to *acetylene* and its many products) and water gas (route to synthetic *methanol* and Fischer-Tropsch products). But when the organic chemist thinks of coking, he is interested mainly in the by-products of the operation which furnish the raw materials for so many aromatic compounds.

6-22 By-product Recovery. The volatile products of carbonization are contained in the *foul gas* which leaves the by-product ovens through

the uptake pipes. At the high temperature (900 to 1100°C) of these pipes, the foul gas consists of a mixture of: (1) permanent gases; (2) condensable vapors of water, ammonia, and various organic compounds including benzene, toluene, and naphthalene; (3) finely divided liquid and solid particles of tar and coal dust. These pass first into the large air-cooled collecting mains and then through water-cooled condensers. Here most of the tar and ammoniacal liquor is condensed and passed to the tar wells for separation. The residual cold gases are passed through mechanical scrubbers to remove the last of the tar; then they go through dilute sulfuric acid to collect the remaining ammonia.¹ Final treatment is in the light-oil recovery plant, whence the gas is passed to storage or burned to heat the ovens.

6-23 Light Oil and Its Products. As coke-oven gas leaves the tar and ammonia scrubbers, it carries about 1 per cent by volume of the vapors of aromatic compounds—chiefly, benzene, toluene, xylenes, and naphthalene. These are removed in the *light-oil recovery plant*. The commonest method is by absorption in a suitable oil, usually a petroleum distillate boiling between 250 and 350°C. The absorbers are tanks filled with wooden grids into which the cooled gas is introduced at the bottom while the cold absorption oil is sprayed in at the top. The rising gas is progressively stripped of its vapors, and the oil, by the time it reaches the bottom, has absorbed 2.5 to 3 per cent by weight of aromatic hydrocarbons. The oil, thus enriched, is passed to a continuous stripping still in which crude light oil (distilling up to about 140°C) is separated from the higher boiling absorption oil. The latter is cooled and returned to the process. The average yield from a ton of coal is about 2.75 gallons of crude light oil, some two-thirds of which is benzene, with smaller amounts of toluenes, xylenes, naphthalene, etc.

Crude light oil is refined in stills provided with efficient fractionating columns that cut the distillate into portions known as crude benzene,² crude toluene, and crude solvent naphtha; naphthalene is recovered from the still tailings. Each distillate is washed with cold sulfuric acid and then carefully refractionated to yield *refined* (technically pure) benzene, toluene, and solvent naphtha, which is mainly a mixture of the three xylenes. All these are used as industrial solvents and for chemical syntheses. The supplies available from coking operations are supplemented—and in some cases exceeded—by production of aromatics from petroleum (Table 6-2).

¹ One ton of coal yields about 22 pounds of ammonium sulfate, a useful nitrogenous fertilizer (Sec. 21-19).

² Benzene and toluene are often called in industry by the German names *benzol* and *toluol*.

6-24 Coal tar is a black, viscous liquid somewhat heavier than water (d , 1.12 to 1.22). Refining consists mainly in fractional distillation. The tar is first run through a preheater or dehydrator where it is exposed in thin layers to a temperature of about 170°C; water and light oil are removed in this operation. The hot tar is then passed to the stills, which are usually of the cylindrical boiler type heated by direct firing. As the temperature rises, the distillate changes in composition and is "cut" into different receivers. Tars from different coals vary in their yields, and operating practice differs among tar distillers, but the figures in Table 6-3 are fairly representative.

TABLE 6-3 COMMERCIAL DISTILLATION OF COKE-OVEN TAR

Distillate	Still temperature, °C	Per cent of tar
Light oil.....	Up to 200	5
Middle or carbolic oil.....	200-250	17
Heavy or creosote oil.....	250-300	7
Green or anthracene oil.....	300-350	9
Pitch (residue left in still).....	62

The *light* oil obtained from coal tar is fractionally distilled. It differs from that obtained from coke-oven gas (which yields most of the benzene and toluene recovered from coking) in its greater content of higher boiling components such as isopropylbenzene and coumarone. The other distillates are treated as follows.

Acidic compounds are extracted (particularly from *middle* or *carbolic* oil) by agitating with a solution of sodium hydroxide, which converts them into water-soluble sodium salts. After settling, the water layer is drawn off and acidified with a mineral acid. The oily liquids which separate are crude *carbolic* acid—from which is obtained phenol (hydroxybenzene, C_6H_5OH)—and *cresylic* acid, a mixture of the cresols (Sec. 8-32).

Basic compounds, containing nitrogen, are extracted in a similar way by agitating the distillates with dilute mineral acids, which convert them into water-soluble salts. The principal products thus obtained are heterocyclic bases (Chap. 26) such as pyridine and methylpyridines.

Neutral compounds, chiefly aromatic hydrocarbons, make up the greater part of all tar distillates. These are isolated—if at all—by differences in physical properties. The *middle* and *heavy* oils, after treatment with alkali and acid as above, are chilled in crystallizing pans for the separation of *naphthalene*, which is then removed by centrifugation and purified by sublimation. Other higher hydrocarbons isolated in appreciable

amounts include methylnaphthalenes, acenaphthene, fluorene, anthracene, and phenanthrene, together with the neutral nitrogen compound carbazole.

6-25 Semirefined Products. Distillates which have been treated for the recovery of acidic and basic compounds and naphthalene are usually run to *creosote oil*. The product sold by this name is any distillate suitable for use in creosoting lumber. Its value depends in part upon its waterproofing effect but mainly upon its content of *tar acids* (phenol, cresols) which are toxic to the wood borer and to fungi.

The residues left in the stills, after varying proportions of volatile matter have been driven off, are sold as *tar* and *pitch*. In volume they often represent 60 to 80 per cent of the tar run to still. Tars are semifluid, while pitch is marketed as soft, medium, and hard, depending on the ease with which it softens on heating. On account of the heavy demand for tar and soft pitch in road building, distillation is often stopped at 270 or 315°C, thus leaving all or a large portion of the anthracene oil in the still residues. Other uses of tar and pitch include the manufacture of roofing and protective coatings for foundations and underground pipes and for similar purposes where waterproofing is necessary.

If any still residue is strongly heated until all volatile products are removed, there is left a residue of very pure *carbon* which has various special uses, such as the manufacture of electrodes.

6-26 Coal Chemicals; Crudes. Section 6-24 names substantially *all* the chemical compounds—about twenty in number—which are recovered industrially as by-products of coking. These compounds, which are *present as such* in coke-oven gas and tar, are called coal chemicals. They are also known as *crudes*. This term does not mean that they are impure when finally isolated and sold; it is used rather to differentiate between them and the many *intermediates* and *finished products* (Sec. 23-1) which are made from them *by chemical reactions*. Some of these reactions have been described in Chapter 5, and others will be considered later, especially in Chapters 23 and 24. This further study will make it clear that **benzene, toluene, and naphthalene** are the three crudes of outstanding importance, from which the great majority of all other aromatic compounds are manufactured.

Hydrogenation Process. As proof for this book is being read in May 1952, announcement is made of a promising, entirely new process in which coal is used for the primary purpose of producing chemicals. This is based on destructive hydrogenation and is conducted by mixing pulverized coal with oil—and, presumably, with selective catalysts—and heating with hydrogen under pressures of the order of 5000 psi. The solid organic matter of the coal is converted largely into liquid products from which, by distillation and other conventional operations, many cyclic organic compounds can be isolated. (After these are removed there remains a heavy oil, part of which is used for mixing with new coal in the first stage.) The yields of benzene, toluene, phenol, naphthalene, etc., per ton of coal are said to be much larger than from coking; relatively large yields are reported also of many other aromatic and heterocyclic compounds (Chap. 26) which are obtained in very small amounts, or not at all, by

conventional methods. The initial installation, in West Virginia, is an eleven-million-dollar "pilot" plant capable of handling 300 to 600 tons of coal a day. If commercially successful, as is expected, much larger plants will doubtless follow.

This method is an adaptation, with many improvements, of the *Bergius process* (1913) which has been used on a considerable scale in Germany for producing gasoline and other liquid fuels by the destructive hydrogenation of low-grade coal.

6-27 Chemical Industry. The market value of all the coal *chemicals* used for the production of other compounds by chemical reactions is just about 1 per cent of the total values of coal-carbonization products (coke, ammonia, etc.). Hence, they are indeed very minor by-products of the coking industry. Similarly, the gaseous hydrocarbons from cracking stills and those extracted from natural gas for chemical use are insignificant in relation to the total petroleum and natural-gas industry. But about a dozen compounds obtained from these combined sources are the major raw materials for a large part of the organic-chemicals industry—an industry which numbers its products by thousands and counts its values in billions of dollars. This multiplication of compounds and of values is accomplished through the practical applications of the science of organic chemistry through the medium of chemical engineering.

CHAPTER 7

MONOHALOGEN DERIVATIVES OF THE HYDROCARBONS

Organic chemistry has been defined as the chemistry of the compounds of carbon. Alternatively, it may be described as the *chemistry of the hydrocarbons and their derivatives*.

A derivative of a particular hydrocarbon is a compound in which one or more of its hydrogen atoms are replaced by other atoms or groups. Thus: C_2H_5Cl , $C_2H_4Br_2$, and C_2H_5OH are derivatives of ethane; $C_6H_5.NO_2$ and $C_6H_5.SO_3H$ are derivatives of benzene; and benzoic acid, $C_6H_5.COOH$, is a derivative of toluene.

Hydrocarbon derivatives are classified for convenient study according to the nature and number of the *functional*¹ groups which they contain. Each type of functional group—*e.g.*, halogen atoms, OH, NO_2 , NH_2 , SO_3H , $COOH$, etc.—carries specific chemical properties which appear in all compounds in which it occurs. It also exerts predictable effects upon physical properties. These characteristics are described in this and the next seven chapters, which deal with the more important types of hydrocarbon derivatives containing a single functional group—*monofunctional derivatives*.

MONOHALOGEN DERIVATIVES OF THE ALKANES

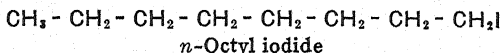
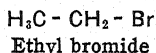
7-1 Alkyl Halides. The monohalogen derivatives of the alkanes are known as alkyl halides, since each of them contains some alkyl group (Sec. 2-24) combined with an atom of halogen. The latter may be either fluorine, chlorine, bromine, or iodine; hence there exist four homologous series of alkyl halides, with the general formulas $C_nH_{2n+1}.Cl$, $C_nH_{2n+1}.Br$, etc. Within each series one observes the usual regularities, such as the progressive changes in physical properties illustrated in Figures 7-1 and 7-2.

Isomerism. We have seen (Sec. 2-25) that propane yields two monobromides—the position isomers 1-bromopropane and 2-bromopropane. As the parent hydrocarbon molecules become larger, opportunities for both chain and position isomerism increase rapidly. Thus the two

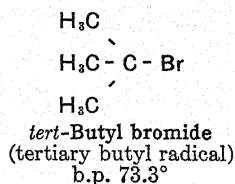
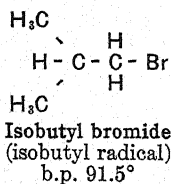
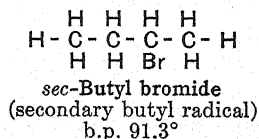
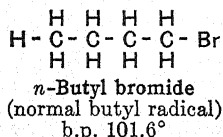
¹ To *function* means to act or operate. When used as a noun, in organic chemistry, a *function* is defined (Webster) as the "characteristic behavior of a compound due to the presence of a particular atom, or group of atoms, or mode of union of atoms; also the atom, group, or arrangement causing such properties."

butanes yield four isomeric monobromides and the three pentanes are capable of yielding eight compounds of the formula $C_5H_{11}X$ for each of the halogens. Beginning with C_4 , an alkyl halide may be *primary*, *secondary*, or *tertiary*, depending on whether the halogen atom is joined to a primary, secondary, or tertiary carbon atom.

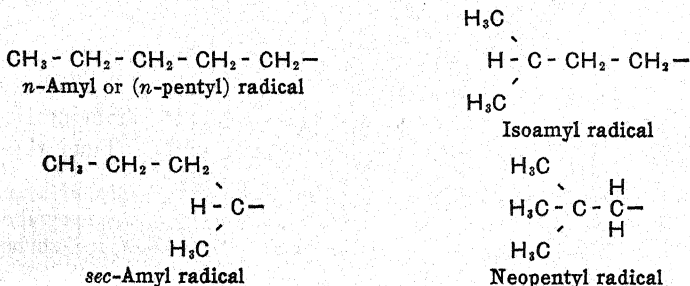
7.2 Nomenclature. In the official system halogen compounds are named as substitution products of their parent hydrocarbons, positions being indicated by numerals in the usual way, *e.g.*, $CH_3.CH_2.CH_2-CHCl.CH_3$ is 2-chloropentane. This method is usually necessary with branched-chain compounds containing five or more carbon atoms. But the official names are often cumbersome, and another system is commoner with the lower halides and with the primary halides derived from higher hydrocarbons with *normal* chains, *e.g.*,



That is, one combines the name of the alkyl radical with the word chloride, bromide, or iodide. The structures of the normal and isopropyl radicals were given in Section 2.25, and those of the four isomeric butyl radicals, C_4H_9 , are shown in the following formulas of the bromides:



The eight radicals of the formula C_5H_{11} , contained in the monoderivatives of the pentanes, are usually called *amyl* rather than *pentyl* radicals. Only four of these are commonly given individual names:



7.3 Physical Properties. The alkyl halides resemble their parent hydrocarbons in that they are colorless liquids, practically insoluble in water and in sulfuric acid, and freely miscible with most organic solvents. Their insolubility in cold sulfuric acid is useful in purifying alkyl halides because one may extract various oxygen-containing compounds—such as alcohols and ethers—by shaking with this acid. Solutions of the alkyl

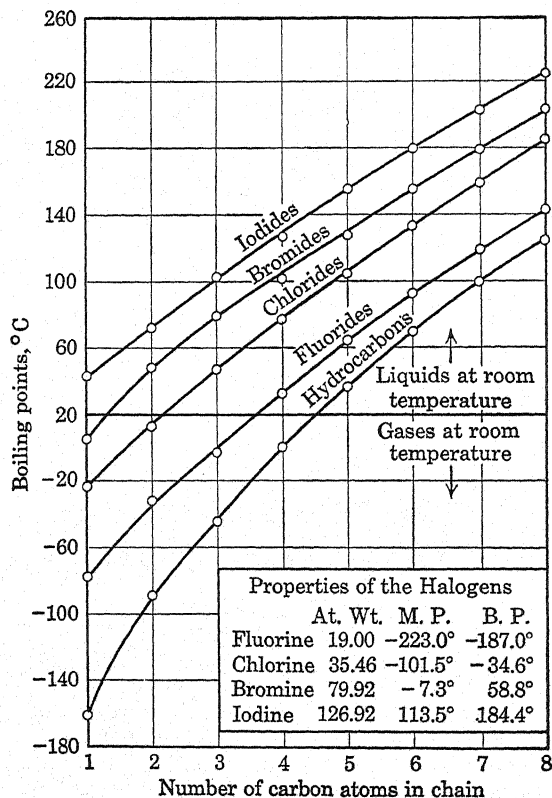


FIG. 7-1 Composition and physical properties; effects of halogen atoms. The boiling points of the normal alkanes and of the corresponding primary alkyl halides are plotted against the number of carbon atoms in the molecule.

halides in organic solvents are practically nonconductors of electricity, showing the absence of appreciable ionization. Measurable dipole moments (Sec. 1.10), such as 1.87 D for methyl chloride, indicate a polarity induced by the electronegative halogen atom; this places a $+\delta$ charge on the carbon atom to which the halogen is joined.

Boiling Points. In Figure 7-1 the boiling points of some of the normal primary alkyl halides and those of their parent hydrocarbons have been

plotted against the number of carbon atoms in the chains. Comparison shows that replacing a hydrogen by any halogen atom produces a marked increase in boiling point and that this increases with the atomic weight of the halogen. In each homologous series boiling points increase with the length of the carbon chain, as among the parent hydrocarbons.

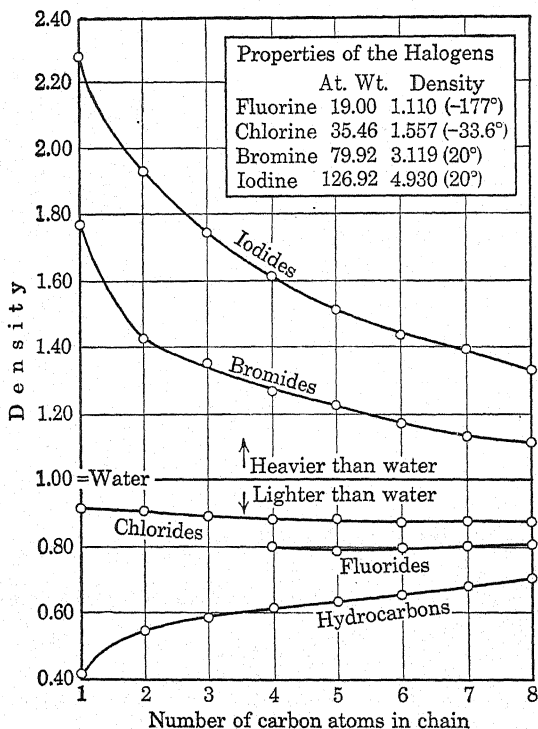
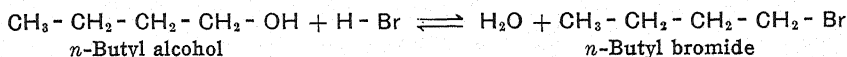


FIG. 7-2 Composition and physical properties; effects of halogen atoms. The densities of the normal alkanes and of the corresponding primary alkyl halides are plotted against the number of carbon atoms in the molecule.

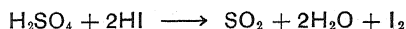
Density. From Figure 7-2 it is apparent that the substitution of halogen for hydrogen raises density and that this effect, also, increases with the atomic weight of the halogen. But in each homologous series, the methyl compound is heaviest and density *decreases* as the carbon chain is lengthened. This can be understood by thinking of the molecule as composed of a lighter-than-water hydrocarbon group (analogous to a fisherman's cork) and a heavy halogen atom (the sinker); in a homologous series the weight of the one halogen atom is constant while the *volume* of the alkyl group, and its consequent buoyant effect, increases more

rapidly than its mass. To put it another way, density is greatest in the compound containing the highest weight percentage of halogen.

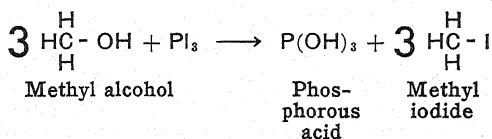
7-4 Preparation. The most general method for making alkyl halides consists in replacing the hydroxyl group of an alcohol by a halogen atom.¹ Alkyl *chlorides* are usually prepared in the laboratory by heating an alcohol with concentrated hydrochloric acid and zinc chloride, or by the action of thionyl chloride, SOCl_2 . The usual method for *bromides* is to heat the alcohol with a mixture of hydrobromic acid and sulfuric acid, the latter helping to bind the water formed in the reaction; *e.g.*,



Iodides cannot be prepared like bromides because the reagents would be destroyed by the reaction

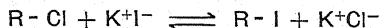


They are usually made by treating the alcohol with PI_3 , which is readily formed by mixing iodine and red phosphorus:



The phosphorus trihalide method can be used also for making bromides and chlorides.

Special Method for Iodides. Alkyl iodides may be prepared by treating a primary alkyl chloride or bromide with a solution of potassium iodide in acetone:



This is an equilibrium reaction but is displaced toward the right by using potassium iodide in excess and by the fact that potassium chloride is only slightly soluble in acetone and precipitates as it is formed.

7-5 Halides from Hydrocarbons. When the corresponding *alkene* is available, an alkyl halide can be made by addition of HCl , HBr , or HI . The usual method is to bring together the dry reactants over a heated catalyst, as was described in the production of ethyl chloride from ethylene (Sec. 3-10). In the similar reaction with propene about 90 per cent of the product is isopropyl chloride, as predicted by the Markownikoff

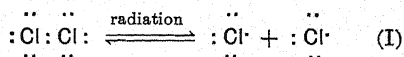
¹ This usual preparation from *alcohols* explains the origin of the term *alkyl*, which is applied both to the organic groups which are thus transferred and to the halides that result.

rule. Wider use of this method is limited by such directing influences and by the fact that not many alkenes are readily available.

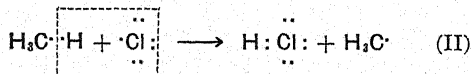
The chief drawback to the manufacture of alkyl chlorides by the chlorination of paraffin hydrocarbons is the impossibility of preventing the formation of polyhalides (Sec. 2·12) which must be separated and marketed. Mention has been made of the successful production of methyl chloride from methane, and at least one plant is producing ethyl chloride from ethane. Probably the most important present application is the chlorination of a mixture of pentane and isopentane obtained from natural gasoline. The formation of dichlorides is minimized by very brief exposure to chlorine in a heated reaction chamber. The industrial product is a mixture of five of the isomeric amyl chlorides, $C_5H_{11}Cl$, all of which boil within a range of about 10 degrees. The mixed chlorides are hydrolyzed by dilute sodium hydroxide to a mixture of the corresponding amyl alcohols (Sec. 8·22).

7·6 Mechanism of Chlorination. It has been mentioned (Sec. 2·4) that chlorine and methane do not react in darkness at ordinary temperatures but that substitution can take place readily in daylight and, above $250^\circ C$, in darkness. These statements describe sufficiently the chlorination of other alkanes. The facts are explained as follows:

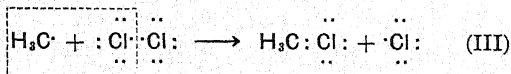
When chlorine gas absorbs energy in the form of light of certain wave lengths, chlorine atoms are formed in low concentration through photodissociation:



Since a chlorine atom carries an unpaired electron, it is essentially a free radical with the high reactivity to be expected. These atoms readily attack alkane molecules in the following manner:



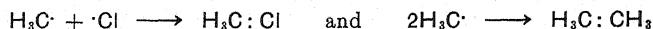
The methyl free radicals thus formed seek stability through electron pairing and find it most readily¹ by attacking molecular chlorine, with the formation of alkyl chloride:



¹ When a methyl free radical is formed in a gaseous mixture of methane and chlorine, it is most likely to collide with a molecule of one of these substances—and only the collisions with chlorine lead to reaction. The probability for collisions between two free radicals is low (see question 6 at the end of this chapter).

Each time (III) occurs, there is liberated a chlorine atom; this can react by (II), which is again followed by (III), and so on, continuously. Thus each chlorine atom formed through photodissociation (I) may start a *chain reaction* (cf. Sec. 6-16) which is capable in theory of propagating itself indefinitely without further illumination. There is strong evidence that some photochlorination chains actually proceed through 100,000 or more molecules.

Sooner or later, however, a chain will be broken through some side reaction which consumes free radicals without generating others. Such *chain-terminating* reactions include those with impurities that may be present and those in which two free radicals unite, *e.g.*,



Continuing illumination during chlorination is therefore necessary.

High-temperature chlorination (above 250°C) is believed to proceed in a similar way, the initiating chlorine atoms being produced by *thermal* dissociation. Chlorination is also strongly catalyzed by the addition of substances capable of furnishing free radicals to start reaction chains. For example, ethane and propane are quickly substituted by chlorine in darkness at 132 to 140°C in the presence of a little tetraethyllead—a well-recognized source of free ethyl radicals. In the absence of such a catalyst to initiate the reaction, no substitution occurs in darkness at this temperature.

7.7 Chemical Properties. Alkyl halides are used mainly as reagents for the laboratory preparation and industrial manufacture of other organic compounds. This use depends upon the wide variety of reactions in which the halogen atom can be replaced and the alkyl group transferred to a new molecule. Such reactions are often called *alkylations* and the organic halides described as *alkylating agents*. The more important reactions of this kind include:

1. The Wurtz-Fittig synthesis (Sec. 2-8).
2. The Friedel-Crafts synthesis (Secs. 5-14; 22-5).
3. The Grignard synthesis (Sec. 7-14).
4. Formation of organometallic compounds (Sec. 14-11).
5. Replacement of halogen by OH to form alcohols, *hydrolysis* (Sec. 7-8).
6. Replacement of halogen by SH to form mercaptans (Sec. 14-9).
7. Replacement of halogen by CN to form nitriles (Sec. 12-16).
8. Replacement of halogen by —O.R to form ethers (Sec. 9-1).
9. Replacement of halogen by —O.CO.R to form esters (Sec. 12-4).
10. Replacement of Cl or Br by I to form iodides (Sec. 7-4).

11. Alkylation of ammonia and amines (Sec. 13.4).
12. The acetoacetic ester synthesis (Sec. 20.17).
13. The malonic ester synthesis (Sec. 20.19).

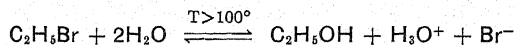
For convenience in reference we may list here also the conversion of alkyl halides into alkenes (Sec. 7.12) and the reaction of many halogen compounds with silver ion (Sec. 7.11), although these cannot be described as alkylations.

Among corresponding halides (*e.g.*, $\text{C}_2\text{H}_5\text{I}$, $\text{C}_2\text{H}_5\text{Br}$, $\text{C}_2\text{H}_5\text{Cl}$, $\text{C}_2\text{H}_5\text{F}$) the order of reactivity in replacement reactions is $\text{I} > \text{Br} > \text{Cl} > \text{F}$. This is the order to be expected from the bond energies which, expressed in kilogram calories per mole, are as follows:

C - I	45.5	C - Br	54	C - Cl	66.5	C - F	107
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Bromides and iodides are ordinarily used in laboratory syntheses on account of their higher reactivity, although they are more expensive. Chlorides are nearly always used in industry; their much lower cost justifies the construction of special equipment in which low reactivity is overcome by working at higher temperatures; ethyl chloride, for example, is used in very large amounts in the manufacture of tetraethyllead. *Primary* halides are most and *tertiary* halides are least satisfactory as alkylating agents.

7.8 Hydrolysis of Alkyl Halides. *Primary* alkyl halides such as ethyl bromide are practically unaffected by cold water. Appreciable hydrolysis occurs on heating with water in sealed tubes



but the rate is slow and the reaction incomplete. *Alkaline hydrolysis* is the practical general method for replacing halogen by hydroxyl. The reaction is more rapid than with water and goes to completion. An industrial application mentioned above is the manufacture of amyl alcohols by heating mixed chloropentanes with 2 per cent sodium hydroxide solution:



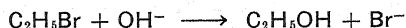
Other reagents, suitable when a low but constant alkalinity is desired, include sodium carbonate solutions and a water suspension of calcium hydroxide—*milk of lime*. Moist silver oxide, which acts as a saturated solution of sparingly soluble Ag^+OH^- , is especially effective for replacing halogen by OH but is entirely too expensive except in research.

Tertiary alkyl halides are hydrolyzed by pure water much more readily than are primary, and this rate is not affected by the presence of either acids or bases. They are also more likely to lose the elements of hydrogen

halide, HX, both with hot water and with many reagents, giving alkenes rather than alcohols (Sec. 7-12). *Secondary* halides are intermediate but, in general, resemble tertiary more closely than primary compounds.

7.9 Mechanism of Alkaline Hydrolysis.

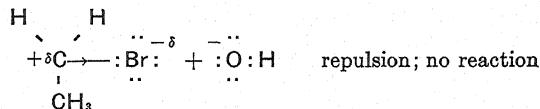
The over-all equation



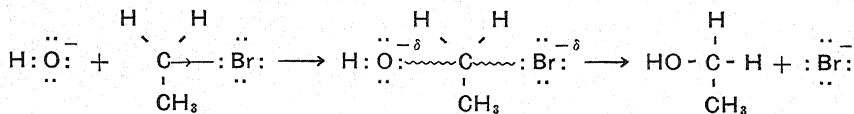
describes *what* happens when ethyl bromide—a typical primary halide—is heated with a dilute alkaline solution but gives no clue as to *how* or *why* the change occurs. Seeking an explanation, we recall that an alkyl halide molecule is polarized in the direction



and that the halogen nucleus is shielded by three unshared pairs of valence electrons. It is most unlikely then that bromine could be removed from $\text{C}_2\text{H}_5\text{Br}$ through any *attraction* exerted upon it by OH^- or another negative ion. In fact, an OH^- ion should be repelled if it happened to approach a $\text{C}_2\text{H}_5\text{Br}$ molecule on the side occupied by bromine:



When, however, OH^- approaches the $+\delta$ carbon atom from the opposite side, it can be *attracted*. On still closer approach, this may develop into a *partial* oxygen-carbon bond. Simultaneously, the bromine atom gains further control of the electron pair which links it to carbon and the bromine-carbon bond likewise becomes partial in character. This is the situation in the *transition state*.¹ If the process continues in the same direction, the oxygen-carbon linkage develops into a typical covalent bond, forming a molecule of ethyl alcohol as a Br^- ion drops off into the solution.



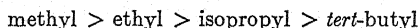
Transition state
(cf. Fig. 17.10)

More direct evidence in support of this mode of reaction is found in the study of certain optically active compounds (Sec. 17·11).

¹ The important theory of the transition state cannot be discussed here in any detail. It must suffice to point out that reactions which can occur in this way are easier because the energy released in forming the new bond helps to supply that which is needed to break the old one.

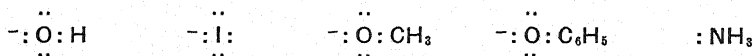
7.10 Nucleophilic Displacements. Alkaline hydrolysis has been discussed in some detail because it is typical of the way in which primary alkyl halides react with a great many different reagents (including reactions 5 through 13 of Sec. 7-7). Each of these follows the same general pattern; that is, the halogen atom is displaced, or substituted, through a rearward ("backside") attack on the $+\delta$ carbon by a reagent which begins to form a new bond while a halide ion is breaking away. Reactions of this kind are brought about by nucleophilic reagents (Sec. 3-9) and for this reason are called nucleophilic displacements.

Effects of Structure. The order of reactivity of the alkyl halides in nucleophilic displacements is

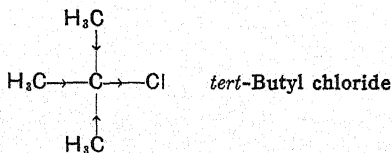


For example if we take as 1.0 the rate at which I^- replaces Cl^- when $\text{C}_2\text{H}_5\text{Cl}$ reacts with K^+I^- in acetone, the rate for $(\text{CH}_3)_3\text{CCl}$ under the same conditions is only 0.0092. This is the order to be expected from the following considerations.

We are assuming that reaction begins with an attack on a $+\delta$ carbon atom by a nucleophilic reagent such as



Such an attack should be most effective when the $+\delta$ charge on a carbon atom is relatively large. We have already seen reason to believe that the methyl group is somewhat electron-releasing as compared with hydrogen. Hence, as H atoms in H_3CCl are replaced by methyl groups, the compounds should become less susceptible to a nucleophilic attack, and least so in *tert*-butyl chloride:

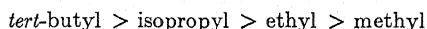


This reasoning is supported by the dipole moment of *tert*-butyl chloride, which is appreciably higher than that of methyl chloride.

Another factor may well be a "space" effect (Sec. 22-14). The space occupied by a methyl group is much greater than that of a hydrogen atom, and it seems probable that three of them, when attached to one carbon atom, may serve as a physical barrier against the rearward approach of a displacing ion. Such a space effect probably explains also why certain primary halides with condensed structures, *e.g.*, isobutyl

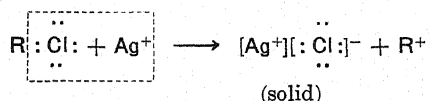
and neopentyl bromides, react very slowly, if at all, by nucleophilic displacement.

7.11 Reactions of Tertiary Halides. The order of reactivity of alkyl halides toward certain reagents is



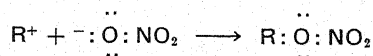
or just the reverse of that described above. This is true, for example, of reaction with silver nitrate in ethanol solution; silver iodide precipitates 90 times faster with $(\text{CH}_3)_2\text{CHI}$ than with CH_3I . It is true, also, of the rate of reaction with water; in ethanol solutions containing some water hydrolysis to the alcohol (at 180°C) is more than 5000 times as rapid with $(\text{CH}_3)_3\text{CBr}$ as with $\text{C}_2\text{H}_5\text{Br}$, and faster than with the primary and secondary isomers of $(\text{CH}_3)_3\text{CBr}$.

These reactions of alkyl halides are with *electrophilic* ions or molecules which, so to speak, *pull* out the halogen atom through a direct attraction for one of its unshared electron pairs:

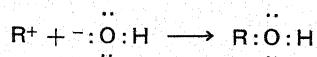


The departing halide ion, Cl^- , carries with it the electron pair which was shared with carbon, and the latter is left with the unit positive charge and the open sextet which characterize a *carbonium ion*. The formula of *tert*-butyl chloride in the preceding section suggests why carbonium ions should be formed most easily when the halogen atom is attached to a *tertiary* carbon; the latter carries the minimum $+\delta$ charge, and a halide ion is most readily detached. Even a polar *solvent*, such as water, can pull out Cl^- , Br^- , or I^- (with increasing ease in this order), which accounts for the rapid hydrolysis of tertiary halides.

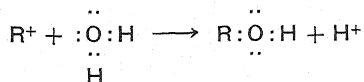
Once the highly reactive carbonium ion is formed, it may react immediately with any negative ion it encounters or with a solvent molecule carrying an unshared electron pair. In the reaction between an alkyl halide and a water-alcohol solution of silver nitrate, one product is an alkyl nitrate (ester of nitric acid):



Some of the alcohol, R.OH , is also formed, either through the reaction of carbonium ion with hydroxyl ion:

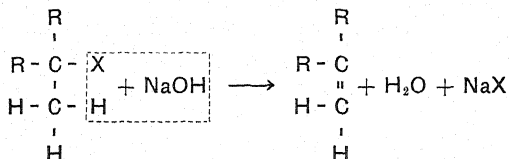


or through an attack on water:

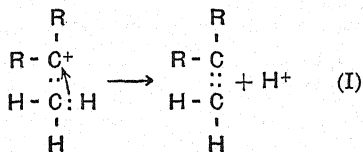


Another way in which a carbonium ion may attain stability¹ is by expelling a proton, thus forming an alkene, as described below.

7.12 Alkenes from Alkyl Halides. The reaction between alkalis and tertiary or secondary alkyl halides has been described already (Sec. 3.6) as a useful laboratory method for establishing the ethylenic double bond. The over-all reaction (*dehydrohalogenation*) consists in the removal of the elements of a hydrogen halide, HX, from adjacent carbon atoms:



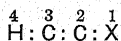
One mechanism, which is especially probable with tertiary halides, is the preliminary formation of a carbonium ion, which stabilizes itself as follows. The carbon atom with the open sextet attracts an electron pair from an adjacent carbon atom; thus a double bond is formed and a proton is released simultaneously:



An alternative mechanism appears more probable in many instances. This involves a nucleophilic attack by hydroxyl upon a *hydrogen* atom;²

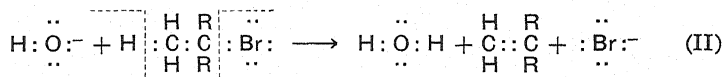
¹ It must suffice here simply to mention the fact that carbonium ions—particularly those of more complicated structures, such as that from a neopentyl halide—are much inclined toward undergoing rearrangements (cf. pinacol rearrangement, Sec. 16.9).

² The hydrogen atom attacked must be one which is situated in position 4 with respect to the halogen atom, in the sense of the scheme



By comparison with Section 10.9 it will be seen that the active hydrogen atom in the aldol condensation occupies this same relative position with respect to another electro-negative atom, oxygen.

as this hydrogen atom is removed to form water, the halide ion X^- , is released simultaneously and the shift of an electron pair establishes the double bond:



7.13 Competitive Reactions. When students begin the "preparation" of organic compounds, they are usually surprised and disappointed at their failure to obtain the expected products in "yields" that even approach the theoretical.¹ Low yields in the organic laboratory are due, in part, to mechanical losses incident to separating a *pure* product. Such losses are relatively greater in small-scale operations than in larger ones—and can be reduced by greater skill and experience in manipulations. But even when it is possible to measure the amount of product *formed*—instead of, as is usual, the amount isolated—the yield may still be poor. This is usually due to one or more of the following causes: (1) failure of the reaction to go to completion because the reverse reaction occurs under the same conditions and an equilibrium is established (cf. Sec. 12.5); (2) a portion of the desired product initially formed disappears through some further reaction before it can be isolated (cf. Sec. 13.4); or (3) a portion of one or both reactants is consumed in some "side reaction" which occurs under the same conditions as the one in which we are interested and, therefore, *competes* with it.

The simultaneous formation of alcohols and alkenes from alkyl halides is one of many examples of competitive reactions (cf. Sec. 8.12). Under this circumstance, the product is necessarily a mixture, the composition of which depends, in part, upon the relative rates of the possible reactions and, in part, upon their equilibrium points if they are reversible. Sometimes it is possible to favor one reaction and increase the yield of its product through a choice of reagent concentration or reaction temperature or by adding a specific catalyst.

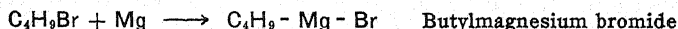
Sometimes, however, the precise *structure* of a compound results in a strong tendency to react in a particular way—a tendency which we may utilize when it serves a purpose but can do little to alter. For example, the following yields of alkene were obtained from typical *primary*, *secondary*, and *tertiary* alkyl bromides in reactions with solutions of sodium hydroxide in dry ethyl alcohol:

¹ This is apt to be true, especially, of students coming from a course in quantitative analysis. They may not have realized that the "inorganic reactions" used there have been selected from a very small number that can be relied upon to give quantitative results.

Alkyl halide	Concentration of NaOH	Yield of alkene, in per cent
Ethyl bromide.....	0.02-2.0 <i>N</i>	0.9 to 1.3
Isopropyl bromide.....	0.05-2.5 <i>N</i>	Up to 80
<i>tert</i> -Butyl bromide.....	0.02-2.5 <i>N</i>	Up to 97

The yields of alkene are given because they were the more easily measured; yields of alcohols¹ are, correspondingly, greatest with primary halides. These differences in the prevailing products go back, of course, to the mechanisms of the reactions which produce them. With ethyl bromide and other primary halides, the prevailing reaction is the exchange of bromide for hydroxyl through the *nucleophilic displacement* reaction on carbon described in Section 7·9. With *tert*-butyl bromide, this mode of reaction is suppressed almost entirely in favor of alkene formation through reaction (I) or (II) of Section 7·12. Reaction proceeds via all these routes with isopropyl and other *secondary* halides, dehydrohalogenation prevailing.

7·14 Grignard² Reaction. A vigorous reaction occurs when an organic halide such as butyl bromide is dissolved in *anhydrous* ethyl ether (Sec. 9·3) and treated with clean magnesium shavings. (Even a trace of water exerts a powerful negative catalytic effect which makes it hard to start the reaction.) The metal dissolves to form an ether-soluble organo-magnesium halide represented by the type formula³ R.Mg.X, *e.g.*,



These compounds, which are always used in the ether solutions in which they are prepared, are known collectively as Grignard reagents. They react readily with a wide variety of other substances, which gives them a position of great importance in organic syntheses. Two reactions are described below and a few of the others (*e.g.*, with aldehydes and ketones,

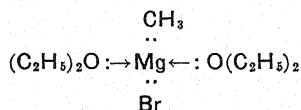
¹ It cannot be assumed from these data that 99 per cent of ethyl alcohol is obtained in such an alkaline hydrolysis of ethyl bromide. The conditions are suitable also for another competing reaction—the formation of ethyl ether by the Williamson synthesis (Sec. 9·1).

² Victor Grignard discovered (1901) the reaction with magnesium which bears his name and later investigated many of its applications. In 1912 he was awarded half of the Nobel prize in chemistry for that year in recognition of the importance of this work. The other half was awarded to another French chemist, Paul Sabatier, for his investigations on catalytic hydrogenation (Sec. 5·12).

³ See Section 14·10 for a statement concerning the nature of the bonds in this and other organometallic compounds.

carbon dioxide, ethylene oxide, anhydrous metallic salts, etc.) in later chapters. The scope of these synthetic reactions is very wide because most organic monohalides will yield a Grignard reagent, though some with difficulty. The principal exceptions are aryl chlorides such as chlorobenzene and those of the vinyl chloride type.

7.15 Grignard Reagents. The ether solutions known as Grignard reagents are more complex systems than the formula $R.Mg.X$ suggests. The ether is not simply a solvent but is coordinated with magnesium, probably as follows:

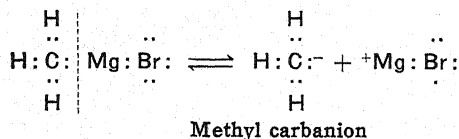
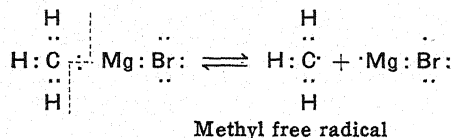


It is also quite certain that there exists an equilibrium in the sense



The position of this equilibrium varies with the natures of the hydrocarbon radical and the halogen (*e.g.*, with $\text{H}_3\text{C.Mg.I}$ it lies far to the left and with $\text{C}_2\text{H}_5.\text{Mg.Cl}$ much farther to the right).

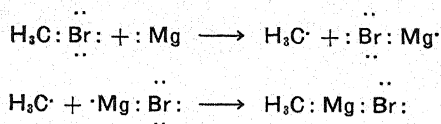
Most of the *reactions* of Grignard reagents are best explained on the assumption that they can serve as potential sources either of *free radicals* or of *carbanions*. These could arise through dissociation of the carbon-magnesium bond in the two ways:



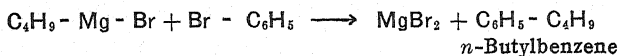
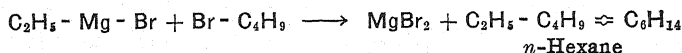
In the usual equation for the formation of Grignard reagents, *e.g.*,



it is seen that the magnesium atom appears to intrude itself between the carbon and halogen atoms. This probably occurs through the following sequence (in which the two valence electrons of the magnesium atom are represented):

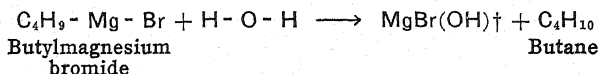


7-16 Synthesis of Higher Hydrocarbons. Grignard reagents react with alkyl halides as illustrated by the following typical equations:



By reactions of this type the Grignard reagents may be used to bring about the union of any pair of hydrocarbon radicals, the same or different and either open chain or cyclic. Thus, like the Wurtz-Fittig and Friedel-Crafts reactions, the Grignard reaction is a general method for the synthesis of *higher hydrocarbons*; it frequently has advantages over the other two.

7-17 Preparation of Corresponding Hydrocarbons. Any Grignard reagent will react rapidly with *water* to form the hydrocarbon corresponding to the halide from which it was prepared, *e.g.*,



This is one of the best ways to obtain *pure* specimens of the lower aliphatic hydrocarbons, and it furnishes the most satisfactory method for replacing a halogen atom by hydrogen. This tendency of Grignard reagents to react with water is another reason why *anhydrous* ether is required in their preparation.

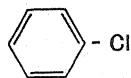
Determination of Active Hydrogen Atoms. Any compound which contains a hydrogen atom attached to *oxygen*, *sulfur*, or *nitrogen* will decompose a Grignard reagent in the same manner as water. This fact imposes a certain restriction on synthetic uses; for example, Grignard reagents may not be used with compounds containing groups such as OH, COOH, NH₂, etc.

But these reactions—destructive to Grignard reagents—are the basis of a useful research method known as the *Zerewitinoff active hydrogen determination*. In this procedure a weighed quantity of an unknown compound and an excess of methylmagnesium iodide are allowed to react under conditions which permit measuring the volume of the methane liberated. Since one molecule of methane is evolved for each *active* hydrogen atom, the results make it possible to calculate how many hydrogen atoms in the compound are attached to oxygen, sulfur, or nitrogen.

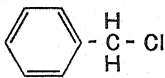
MONOHALOGEN DERIVATIVES OF CYCLIC HYDROCARBONS

7-18 Chlorobenzene, benzyl chloride, and cyclohexyl chloride are typical and the best known examples of three distinct types of halogen compounds derived from cyclic hydrocarbons:

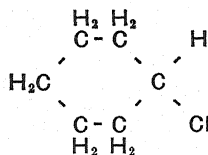
† Probably the inorganic product is actually a mixture of MgBr₂ and Mg(OH)₂. The "basic-salt" formula used here is convenient in balancing equations.



Chlorobenzene
Phenyl chloride



Benzyl chloride
 α -Chlorotoluene

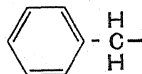
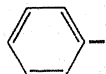


Cyclohexyl chloride
Chlorocyclohexane

Chlorobenzene and other compounds in which a halogen atom is attached to a *nuclear* carbon atom are *aryl* halides. Benzyl chloride is the most important member of that class of aromatic compounds in which a halogen atom is joined to an extranuclear or *side-chain* carbon; these are sometimes called *aralkyl* halides. Cyclohexyl chloride illustrates the halides derived from *alicyclic* hydrocarbons.

The student should note carefully the difference between the names *phenyl* and *benzyl* which are given to the following cyclic groups or radicals:

Phenyl radical
 $\text{C}_6\text{H}_5\text{-}$



Benzyl radical
 $\text{C}_6\text{H}_5\text{-CH}_2\text{-}$

7.19 Aryl Halides. Aryl chlorides and bromides are usually made from the aromatic hydrocarbons by direct substitution of hydrogen by chlorine or bromine with iron as a catalyst. Another method is the diazo reaction (Sec. 13.17), which is most useful in the preparation of iodides and fluorides. The method of preparing alkyl halides by replacement of an alcoholic hydroxyl group is *not* applicable because aryl hydroxides (phenols) do not react in this way either with hydrogen halides or with phosphorus halides. Solubility relations are similar to those of the alkyl halides. Boiling points and densities increase as expected with the atomic weight of the halogen (Table 7.1).

TABLE 7.1 MONOHALOGEN DERIVATIVES OF BENZENE

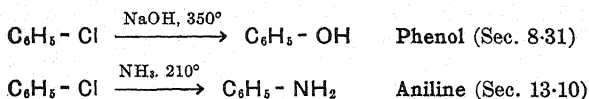
	Boiling point, $^{\circ}\text{C}$	d
Benzene.....	80.1	0.879
Fluorobenzene, $\text{C}_6\text{H}_5\text{F}$	83	1.024
Chlorobenzene, $\text{C}_6\text{H}_5\text{Cl}$	132.1	1.107
Bromobenzene, $\text{C}_6\text{H}_5\text{Br}$	156.2	1.497
Iodobenzene, $\text{C}_6\text{H}_5\text{I}$	188.6	1.838

7.20 Chlorobenzene is the aryl halide of major importance. It is manufactured in large quantities by adding iron filings to dry benzene and

passing in chlorine, at a rate which keeps the temperature between 40 and 60°C, until a sample of the reaction mixture shows the desired increase in density. The product yields on fractional distillation a little unreacted benzene (b.p. 80.1°C), about 80 per cent of chlorobenzene (b.p. 132.1°C), and some 15 per cent of a high-boiling (170 to 177°C) residue consisting chiefly of *p*-dichlorobenzene with a smaller amount of its *ortho* isomer.

Replacement of Halogen. Halogen attached to nuclear carbon is *much less reactive* than in an alkyl halide. The chlorine atom of chlorobenzene does not enter into the Friedel-Crafts reaction, and the compound does not react to form a Grignard reagent;¹ boiling with alcoholic potash fails to split out a recognizable amount of chlorine. Hence, chlorobenzene and other simple aryl chlorides are of little value for laboratory syntheses depending on halogen replacement. The origin of the low reactivity of the chlorine atom is considered in Section 22-9.

Industrially, large amounts of chlorobenzene are used for the manufacture of phenol and aniline:



The success of these methods for replacing the chlorine atom depends on the construction of industrial equipment capable of withstanding corrosion by the reactants and the high pressures developed at the necessary working temperatures. The reactivity of all chemical compounds is increased by heat, and many reactions can thus be brought about efficiently which either do not occur, or are too slow to be useful, at the temperatures obtainable in open vessels or in laboratory pressure equipment.

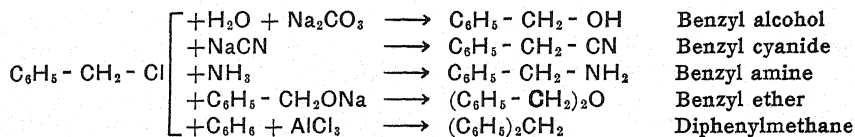
Nuclear Reactions. The *ortho* and *para* hydrogen atoms of chlorobenzene can be replaced by further chlorination, by nitration, etc. (Secs. 23-5ff). But these reactions proceed less rapidly than with benzene, showing that the halogen atom attached to the ring is deactivating. This exception to the usual activating effect of *ortho*- and *para*-directing groups is discussed in Section 22-9.

7-21 Benzyl chloride, $\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$, is manufactured by the side-chain chlorination of toluene (Sec. 5-15) in the absence of iron and such other

¹ The formation of phenyllithium and similar aryllithium compounds, which can be used for many of the same purposes as the Grignard reagent, is described in Section 14-11. Bromobenzene reacts with magnesium in dry ether to form $\text{C}_6\text{H}_5\text{MgBr}$, but more slowly than benzyl chloride and alkyl halides.

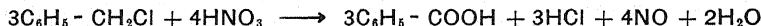
catalysts as favor nuclear substitution. It is a colorless liquid (b.p. 179.4°C; *d.* 1.100); its vapors are strongly irritating to the eyes.¹

In sharp contrast with chlorobenzene and other *aryl* halides, benzyl chloride enters into many displacement reactions even more readily than alkyl halides. Hence it is used widely in organic syntheses, both in the laboratory and industrially, for introducing the benzyl radical into other compounds, *e.g.*,

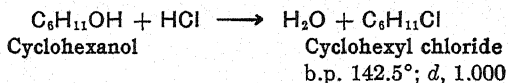


This high reactivity is observed generally with halogen on a side-chain carbon *adjacent* to the aromatic nucleus.

The chloromethyl side chain of benzyl chloride is oxidized like the methyl side chain of toluene and yields the same organic product, benzoic acid:



7-22 Alicyclic Halides. Cyclohexyl chloride is formed, together with polysubstitution products, by the action of chlorine on cyclohexane, but it is best obtained by heating cyclohexanol with concentrated hydrochloric acid:



It enters into the replacement reactions of the alkyl halides with about the same ease as the corresponding open-chain compounds, *e.g.*, 2-chlorohexane. Like secondary alkyl halides it rather easily loses a molecule of hydrogen chloride to form an ethylenic double bond. The alicyclic monohalides (cf. Sec. 23-2) have little present importance.

DETECTION AND IDENTIFICATION OF HALOGEN COMPOUNDS

7-23 Detection of Halogen. The customary tests for halogen in non-carbon compounds are actually tests for chloride, bromide, and iodide *ions* in their aqueous solu-

¹ The property of causing involuntary weeping is characteristic of many halogen compounds, particularly aromatic compounds with halogen in a side chain, such as benzyl bromide, bromobenzyl cyanide, $\text{C}_6\text{H}_5\text{CHBr}(\text{CN})$, and bromine-substituted xylenes. These compounds were used as lachrymators, or *tear gases*, during the First World War and have since been used in grenades by police. One of the most effective and important is chloroacetophenone, $\text{C}_6\text{H}_5\text{COCH}_2\text{Cl}$.

tions. Most organic halogen compounds are practically insoluble in water and non-ionized even when dissolved (*e.g.*, in dilute alcohol). Consequently, before the presence of halogen in an organic compound can be either denied or affirmed, a treatment sufficiently drastic to break any halogen-carbon linkage is necessary.

Beilstein Test for Halogen. This test is performed by heating a spiral of copper wire in a colorless flame until it is coated with cupric oxide; the cooled spiral is dipped into the substance to be tested and returned to the flame; as the adhering organic compound is burned, a portion of any halogen present is converted into a copper halide which volatilizes and imparts, briefly, a green color to the flame. This is a useful exploratory test for differentiating rapidly between compounds which do and those which do not contain halogen; if a positive result is obtained, the sodium fusion must be made in order to distinguish between chlorine, bromine, and iodine.

Sodium Fusion Test. In this procedure the organic molecule is disrupted by fusing a small portion of the substance with metallic sodium; any halogen present is converted into a sodium halide. The cooled melt is dissolved in water and filtered from particles of carbon. The filtrate, which should be water-white if the fusion has been satisfactory, is divided into several small portions for the different tests required.¹ One portion is acidified with HNO_3 and AgNO_3 is added; a precipitate of silver halide shows the presence of one of the halogens. To distinguish between them, another portion of the solution is acidified and treated with chlorine water and carbon bisulfide, as in the usual procedure of inorganic qualitative analysis for distinguishing between chloride, bromide, and iodide ions.

7-24 Classification Tests.² The firmness with which halogen is bound is a useful further guide in the identification of a compound containing it. So-called *ionizable halogen* may be detected by shaking a portion of the substance with cold distilled water and adding dilute nitric acid and silver nitrate. The *pure* compounds most likely to give precipitates of silver halide in this test are halogen acid salts of amines (Chap. 13) and readily hydrolyzed acid chlorides (Chap. 12). *Loosely combined halogen* may be tested for by adding an ethanol solution of silver nitrate to a drop of the substance and noting whether silver halide is precipitated after standing a few minutes at room temperature or, if not, after boiling. If this test is negative, the substance should be treated with a solution of potassium iodide in dry acetone, looking for a precipitate of potassium bromide or chloride (Sec. 7-4). Most aliphatic, alicyclic, and aralkyl halides respond more or less rapidly to one or both of these tests. Chlorobenzene and other aryl halides do not respond unless the molecule contains also groups such as NO_2 in positions which activate the halogen atom (Sec. 22-13).

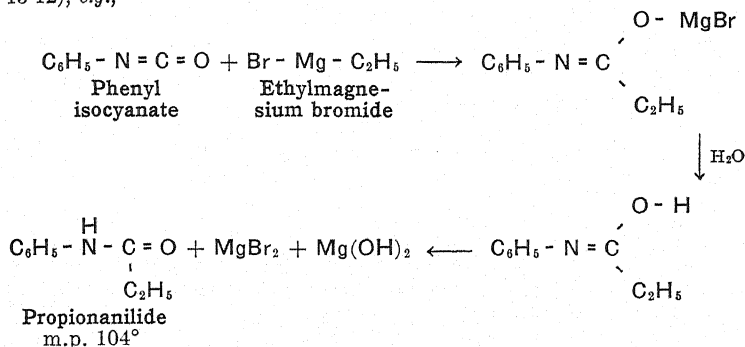
7-25 Derivatives. Many *aromatic* halogen compounds can be nitrated to give definite nitro compounds that are suitable derivatives for final identification; if a side chain is present, it is often possible to oxidize to a readily recognizable acid; otherwise, it may be necessary to establish identity by accurately determining and comparing two or more physical constants.

Solid derivatives of *alkyl* halides are best prepared through the Grignard reaction. The Grignard reagent from any alkyl halide will react by addition with phenyl

¹ If the substance under examination contains nitrogen or sulfur, the filtrate will contain NaCN or Na_2S and separate portions may be tested for the CN^- and S^{2-} ions. Hence a single fusion suffices to show the presence or absence of all the elements for which tests are ordinarily required.

² For a more adequate discussion of these tests than is possible here, consult Shriner and Fuson, "The Systematic Identification of Organic Compounds" John Wiley & Sons, Inc., New York, 1948, 3d ed., pp. 121*ff.*, 140*ff.*

isocyanate; when treated with dilute acid, the product is converted into an *anilide* (Sec. 13-12), *e.g.*,



α -Naphthalides are obtained in like manner, using α -naphthyl isocyanate. Primary and secondary alkyl halides can also be converted through their Grignard reagents into corresponding alkylmercuric halides (Sec. 14-11).

Questions

1. (a) Explain the difference between primary, secondary, and tertiary alkyl halides, giving structural formulas to illustrate. (b) Write the structural formulas of the following radicals: *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-amyl, isoamyl, neopentyl.

2. In which of the following physical properties does ethyl bromide resemble ethane? Make comparisons when there is any marked difference: (a) color; (b) solubility in water and water solutions; (c) solubility in organic liquids; (d) solubility in sulfuric acid; (e) boiling point; (f) density; (g) dipole moment.

3. (a) Name the alkyl halides that are gases under ordinary laboratory conditions. (b) Which are lighter than water? (c) Summarize the effects of the nature of the halogen and of increasing chain length on the boiling points and densities of alkyl halides.

4. Show by structural equations the preparation of isopropyl bromide from isopropyl alcohol, $\text{CH}_3\text{CH}(\text{OH})\text{CH}_3$, by two general methods.

5. What alkyl bromides would be formed by addition of hydrogen bromide to the following hydrocarbons? If more than one product might be formed, indicate this and tell which predominates under peroxide-free conditions (Sec. 3-11): (a) ethylene; (b) propene; (c) 1-butene; (d) 2-butene; (e) isobutylene.

6. A mixture of one mole each of chlorine and ethane is illuminated enough to produce a moderate rate of reaction. Recall that one mole of any compound contains 6×10^{23} molecules, and assume that a few hundred molecules of Cl_2 are dissociated into atoms through absorption of light. Explain in terms of probable encounters why the formation of ethyl chloride by the *chain reaction* described in Section 7-6 should predominate over any side reactions to be expected.

7. The ethoxide ion, $\text{C}_2\text{H}_5\text{O}^-$, formed by the action of sodium on ethyl alcohol, is a nucleophilic reagent which reacts in many ways like the hydroxide ion. Indicate how it should react with *n*-propyl bromide, showing a transition state and the final product to be expected.

8. It has been shown that when 2-iodooctane (*sec*-octyl iodide) is dissolved in an acetone solution of potassium iodide containing the radioactive isotope of iodine, the

organic compound acquires radioactivity. Account for this fact in terms of a nucleophilic displacement. (Suggestion: Indicate a radioactive iodine atom by a special symbol such as *I.)

9. Write equations for two reactions that *may* occur when each of the following compounds is heated with an alkaline solution: ethyl bromide, isopropyl bromide, *tert*-butyl bromide, and *n*-hexyl bromide.

10. (a) With which of the compounds just listed is alkene formation most likely to occur? (b) Which would be expected to give the best yields of the corresponding alcohols?

11. Explain accurately why *tert*-butyl bromide forms carbonium ions and an alkene more readily than any of its isomers.

12. (a) Define the term "Grignard reagent." (b) Write structural equations for the preparation of isopropylmagnesium bromide and for the reactions of the latter with ethyl bromide and with water.

13. Construct a chart, centering about the formula of ethyl bromide, on which you give structural equations and specify reagents and necessary conditions for: (a) the preparation (or formation) of ethyl bromide from ethane, ethylene, and ethyl alcohol; (b) the conversion of ethyl bromide into each of these three compounds; (c) two methods for passing from ethyl bromide to *n*-butane and three methods for passing to ethylbenzene.

14. Write the structural equations and specify the necessary conditions for the manufacture of: (a) chlorobenzene; (b) phenol and aniline from chlorobenzene.

15. From the rules of directing influences (Sec. 5-19), write the structural formulas of the chief products to be expected from (a) the mononitration of chlorobenzene; (b) the dinitration of chlorobenzene; (c) the mononitration of *p*-dichlorobenzene; (d) the further chlorination of a mixture of *o*- and *p*-dichlorobenzene.

16. When bromobenzene is dissolved in anhydrous ether and magnesium is added with the object of preparing a Grignard reagent, there is always some loss through the formation of biphenyl, $C_6H_5.C_6H_5$. Explain.

17. Write structural equations and indicate the necessary experimental conditions for making: (a) benzyl chloride from benzyl alcohol; (b) benzyl chloride from toluene; (c) *p*-bromobenzyl chloride from toluene.

18. What products would be expected from the oxidation of: (a) benzyl chloride; (b) *p*-chlorotoluene; (c) *p*-chlorobenzyl bromide; (d) *p*-bromobenzyl chloride; (e) 2,4-dichlorobenzyl bromide.

19. Compare the behavior of isopropyl chloride, chlorobenzene, benzyl chloride, and cyclohexyl chloride under the following conditions, writing structural equations for all reactions to be expected: (a) heating with sodium shavings; (b) treatment with benzene and anhydrous $AlCl_3$; (c) dissolving in dry ether with addition of magnesium shavings; (d) heating under reflux with sodium carbonate solutions.

20. Give the electronic mechanisms of the following reactions, making clear the exact differences: (a) the Wurtz-Fittig synthesis; (b) the photochlorination of an alkane; (c) the formation of an alkyl halide from an alkene (Sec. 3-10); (d) the alkaline hydrolysis of a primary alkyl halide; (e) alkene formation from a tertiary halide.

21. (a) Describe how *inorganic* chlorides, bromides, and iodides are tested for the presence of halogen. (b) Will this test detect halogen in such compounds as potassium chlorate? Explain. (c) Why does this method of testing give negative results with many organic compounds containing halogen? (d) What is the fundamental purpose of a sodium fusion made before testing an organic compound for the presence of halogen?

22. An organic compound has been shown to contain chlorine, but no precipitate of silver halide is obtained when a portion is shaken with a water solution of silver nitrate. What inference as to its structure may be drawn if *one* of the following additional observations is made: (a) When a specimen is warmed with an ethanol solution of silver nitrate, AgCl is precipitated? (b) There is no response to the silver nitrate test but KCl is precipitated when the compound is treated with an acetone solution of potassium iodide? (c) Both these tests are negative?

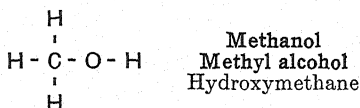
CHAPTER 8

ORGANIC HYDROXIDES; ALCOHOLS AND PHENOLS

Organic compounds containing one or more hydroxyl groups are very numerous, and many are of great importance. They include derivatives of all types of hydrocarbons. Those in which the hydroxyl group is attached *directly* to carbon of an aromatic nucleus are known as *phenols*; all other hydroxyl derivatives of hydrocarbons are called *alcohols*.

ALCOHOLS

8.1 Structure. The simplest substance having the properties of an alcohol is *methanol* or *methyl alcohol*, CH_4O . Giving the atoms their usual valences, only one structure is possible and the compound can be described as hydroxymethane:



For *ethyl alcohol*, $\text{C}_2\text{H}_6\text{O}$, valence relations are satisfied equally well by two different structural formulas:



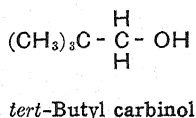
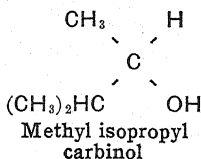
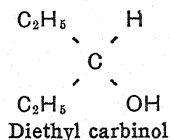
Ethyl alcohol closely resembles methanol in its chemical properties, and this is a strong argument for a similar structure, *i.e.*, for the hydroxide structure shown in (I). Further evidence is furnished by a reaction between sodium and ethyl alcohol in which one, *but only one*, hydrogen atom is displaced. From that fact it is concluded that one of the six hydrogen atoms is attached in a manner different from the other five. No such difference is indicated by (II), in which all the hydrogen atoms are joined to carbon in the same way, but it is suggested at once by (I).

8.2 Homologous Series of Alcohols. Many compounds are known which, for reasons similar to those just given, must be regarded as monohydroxy derivatives of the alkanes. All these belong to the homologous series of monohydric alcohols of the general formula $\text{C}_n\text{H}_{2n+2}\text{O}$ or $\text{C}_n\text{H}_{2n+1}\text{OH}$, of which CH_3OH and $\text{C}_2\text{H}_5\text{OH}$ are the simplest members.

These alcohols exhibit the relations which are usual among homologues. Boiling points rise progressively with increasing chain length (Fig. 8·1). All are liquids up to lauryl alcohol (dodecanol, $C_{12}H_{25}OH$), which melts at $24^{\circ}C$, and all are lighter than water.

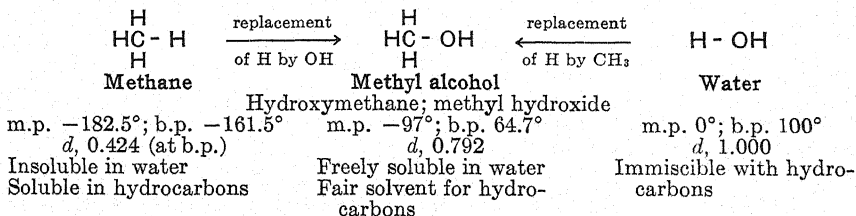
Nomenclature. The systematic names of the alcohols are formed from those of the parent hydrocarbons by changing the terminal *-e* to *-ol* and indicating the position of the OH group by the appropriate numeral. The common names of the simpler compounds are formed by adding the word *alcohol* to the name of the alkyl radical that it contains.

Carbinols. Branched-chain alcohols are sometimes named as substitution products of methanol. In these names the residue of methanol ($C-OH$, with any hydrogen atoms that may be attached to the carbon) is designated by the word *carbinol*, *e.g.*,



Isomerism. Two propyl, four butyl, and eight amyl (pentyl) alcohols are known, corresponding to the isomeric radicals described in Section 7·2. These include *primary*, *secondary*, and *tertiary* alcohols. Above C_5 , many isomers are possible but relatively few are known.

8·3 Structure and Properties. It is convenient to think of the monohydric alcohols as being derived from hydrocarbons by the replacement of one hydrogen atom by a hydroxyl group. But, with equal propriety, they may be regarded as derived from *water* by replacing one hydrogen atom by a hydrocarbon radical, *e.g.*,



Methanol inherits properties from both parents—methane and water. The methyl radical carries with it the combustible property of methane; the reaction with sodium is just as clearly acquired—along with the hydroxyl group—from the other parent, water. In melting point, boiling point, density, and solubility relations methanol lies between the two but more closely resembles water. Hence, the hydroxyl group must be

regarded as having more influence than the methyl radical in determining the physical properties of this alcohol.

As the bulk of the hydrocarbon radical increases—*i.e.*, on ascending the series—its properties become more marked while those derived from water decrease progressively. For example cetyl alcohol, $C_{16}H_{33}OH$, is a solid (m.p. $49.3^{\circ}C$) which is greasy to the touch, insoluble in water, burns with a smoky flame, and generally resembles paraffin wax.

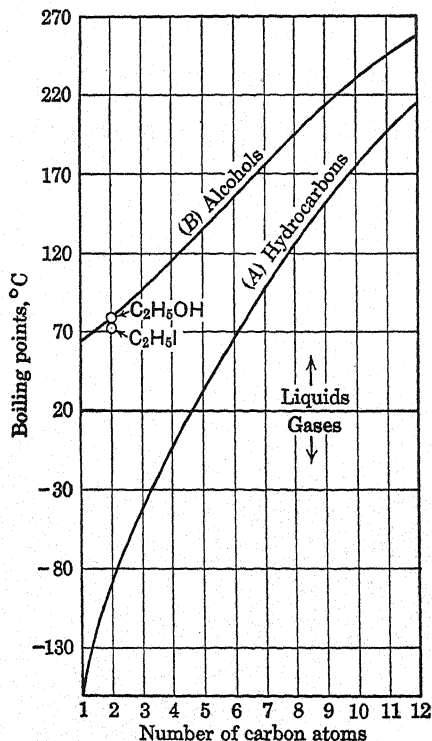


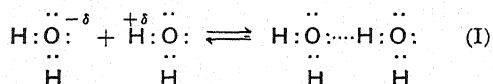
FIG. 8-1 Structure and physical properties. Effects of introducing the hydroxyl group as shown by the relative boiling points of the normal alkanes (A) and the corresponding primary alcohols (B).

Boiling points of the normal alkanes and those of the corresponding primary alcohols have been plotted in Figure 8-1. Comparison of the curves shows that replacement of a hydrogen atom by OH causes a very marked increase in boiling point. This cannot be explained by the increase in molecular weight, as may be seen by comparing the boiling point of ethyl alcohol with that of ethyl iodide, which is shown in Figure 8-1 for this purpose. The change from C_2H_6 to C_2H_5O adds only 16 units in molecular weight, while the change from C_2H_6 to C_2H_5I adds 126 units—nearly eight times as much—yet the boiling point of ethyl alcohol is

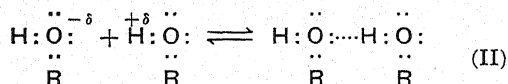
somewhat higher. This and other similar facts are explained by molecular association of the alcohols.

8-4 Association; Hydrogen Bonds. The alcohols, water,¹ and certain other liquids with boiling points abnormally high for their molecular weights are described as *associated*. This implies that in the liquid state single molecules are united in more-or-less stable complexes of the types $(C_2H_5OH)_n$, $(H_2O)_n$, etc. The abnormally high boiling points observed are due to the heat which must be supplied to disassociate these complexes to such an extent that the vapor pressure of single molecules equals the atmospheric pressure, as is necessary for boiling. Molecular association of water and the alcohols is now ascribed to hydrogen bonding.

Hydrogen Bonds. Owing to the difference in electronegativity (Sec. 1-9) the oxygen atom in water carries a relatively high $-\delta$ charge and the hydrogen atoms are correspondingly positive. This and the bond angle (see Fig. 1-5) account for the observed dipole moment of 1.84 D. Furthermore, the oxygen atom has two unshared electron pairs. Attraction between a $+\delta$ hydrogen atom of one molecule and an electron pair on the $-\delta$ oxygen atom of another establishes a *hydrogen bond* (or *hydrogen bridge*) which holds them together in the twin $(H_2O)_2$ molecule:



Alcohol molecules, $R.OH$, associate in the same way:



It is apparent that the oxygen atom shown at the extreme right in (I) and (II) should be able to unite in like fashion with a third molecule of water or alcohol. Theoretically, this might continue indefinitely; actually, association does not result in the formation of giant molecules because some hydrogen bonds are broken by molecular impacts as others are being formed.

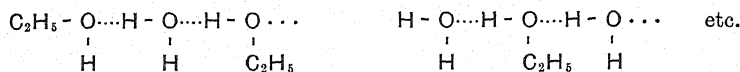
The hydrogen bond is not an ordinary covalent linkage, for we know beyond reasonable doubt that the hydrogen atom is incapable of taking four electrons into its valence shell. The bond is made possible by the positive charge and the *minute size* of the proton, which appears to embed itself in the electron clouds of two oxygen atoms and hold them closer than they could otherwise approach. The only hydrogen bonds strong

¹ The molecular weight of water in the form of steam is 18, corresponding to the simple formula H_2O . The fact that water boils at 100°C is arresting when we compare it, for example, with methane (mol. wt. 16, b.p. -161.5°C) or oxygen (mol. wt. 32, b.p. -183°C).

enough to produce significant effects are between atoms of fluorine, oxygen, and nitrogen (*e.g.*, F—H—F, O—H—O, N—H—F, N—H—O, N—H—N), that is, the most highly electronegative elements.

8.5 Solubility Relations. Methyl, ethyl, and a few other alcohols of low molecular weight are miscible with water in all proportions; butanol¹ and the amyl alcohols are only partially miscible (Sec. 8.6); from C₆ upward, solubility in water approaches the practical zero of the parent hydrocarbons. Conversely, butanol and higher alcohols are better solvents for hydrocarbons than are methanol and ethanol.

Miscibility of the lower alcohols with water is due largely to hydrogen bonding between OH groups of the two kinds of molecules, *e.g.*,



This permits mutual mixing when the hydrocarbon radicals are *small*. But when the hydrocarbon group is as large as hexyl, water molecules are able to make fewer contacts with alcoholic OH groups, and the water layer, with its molecules held together by dipolar attractions and hydrogen bonds, resists penetration by the bulky, nonpolar C₆H₁₃ groups.

A rough but useful guide to solubility relations in general is the statement that *like dissolves like*. The most important "likeness" in molecules, so far as solubility relations are concerned, is in their polarities. Polar liquids in general, and especially when they are capable of hydrogen bonding, mix with each other and dissolve salts and other polar solids. Conversely, the best solvents for nonpolar compounds are usually hydrocarbons or other liquids of little or no polarity.

8.6 Separation from Water. When a partially miscible alcohol is shaken with water until equilibrium is established, two layers separate on standing. Their compositions are illustrated by the following data, expressed in percentage by weight:

	Water layer, saturated solution of alcohol in water		Alcohol layer, saturated solution of water in alcohol	
	Per cent water	Per cent alcohol	Per cent water	Per cent alcohol
<i>n</i> -Butyl alcohol (20°).....	92.2	7.8	20	80
Isoamyl alcohol (15°).....	97.3	2.7	9.3	90.7

¹ It is interesting to note that *tert*-butyl alcohol is freely miscible with water whereas the solubility of its three isomers is only around 10 per cent. This is a somewhat extreme illustration of a general rule that chain branching increases solubility.

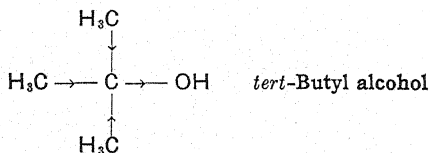
These figures show that more water enters the alcohol layer than vice versa. The difference is made more striking by converting the data to mole fractions. This discloses that the "water" layer contains only about 1 butanol molecule to 50 of H_2O ; in the "alcohol" layer, the ratio is very close to 1:1.

To separate an alcohol from its *solution in water*, it is customary to take advantage of the fact that the water solubility of most organic compounds is greatly decreased when the solution is saturated with an inorganic compound. This procedure is known as "salting out." In order to separate an alcohol, the aqueous solution may be saturated with sodium chloride, anhydrous potassium carbonate, or sodium hydroxide. The fact that the miscibility of the alcohols with water is *decreased* by the presence of sodium hydroxide is an important difference from the behavior of phenols.

The *alcohol* layer that separates when any partially miscible alcohol has been in contact with water is actually a saturated *solution of water in the alcohol*. Ethyl and many other lower alcohols form constant-boiling (azeotropic) mixtures with water, hence, the latter must be removed otherwise than by fractional distillation. Usually some dehydrating agent is used, *e.g.*, solid sodium hydroxide, quicklime, anhydrous K_2CO_3 or CuSO_4 . Calcium chloride *must not be used* for drying alcohols since it forms with them molecular complexes of the nature of hydrates, *e.g.*, $\text{CaCl}_2 \cdot (\text{C}_2\text{H}_5\text{OH})_x$.

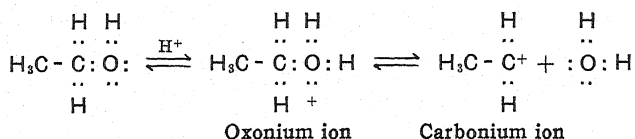
REACTIONS OF ALCOHOLS

8.7 Alcohols react to form alkyl halides, esters of many acids, ethers, alkenes, and alkoxides. They are much more easily oxidized than are the saturated hydrocarbons from which they are derived. All these reactions center about the hydroxyl group and the carbon atom to which it is attached. Marked differences are observed, depending on whether this atom is primary, secondary, or tertiary. Many of these differences can be related to the decreasing $+\delta$ charge on the hydroxylated carbon atom as the hydrogen atoms in methanol are replaced by electron-releasing alkyl groups. This charge is least in a *tertiary* alcohol:



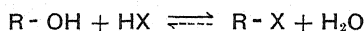
8.8 Reactions with Acids. We have seen that the oxygen atom of an alcohol tends to use one of its unshared electron pairs to form a hydrogen bond with another molecule of an alcohol or with water. Acting in a similar way toward any strong acid (a compound which readily donates a proton) the oxygen atom of an alcohol gets full possession of a proton

and readily forms an *oxonium*¹ ion. The +1 charge on oxygen in this ion favors the separation of a molecule of water and the formation of a carbonium ion, *e.g.*,



The over-all reactions of alcohols in the presence of strong acids are best interpreted as results of further reactions of highly electrophilic carbonium ions formed in this way.

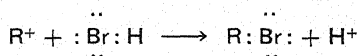
8-9 Conversion to Alkyl Halides. The reaction of alcohols with hydrogen halides (halogen acids), which has been described (Sec. 7-4) as the most general method for preparing alkyl halides, is usually represented by an over-all equation of the type



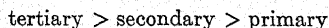
We may now interpret it as consisting of the formation of a carbonium ion, in the manner just explained, followed by union of the electrophilic carbonium ion with a halide ion:



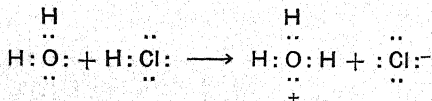
or an attack on a molecule of hydrogen halide:



The *rate* at which OH is replaced by halogen varies widely with the structure of the alcohol. *Primary* alcohols, such as butanol, require refluxing with concentrated hydrochloric acid containing zinc chloride. But when *tertiary* butyl alcohol and concentrated hydrochloric acid are mixed at room temperature, *tert*-butyl chloride begins to form immediately, as evidenced by prompt clouding of the mixture and an early separation into two layers. The rate with *secondary* alcohols is intermediate but closer to that of the tertiary compounds.² This order of reactivity

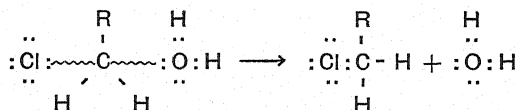


¹ The simplest possible oxonium ion is the so-called *hydronium* ion which is formed whenever any acid ionizes in water, *e.g.*,

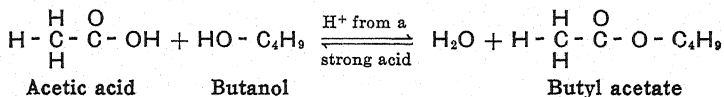


² These differences in rates are utilized in the Lucas test (Sec. 8-35) for differentiating between the three classes of alcohols.

is the order of the ease with which carbonium ions are formed by reaction with the acid. It is greatest with a tertiary alcohol, in which the low $+\delta$ charge on carbon is most favorable to separation of a molecule of water from the oxonium ion. It seems probable that the slow reaction with primary alcohols occurs through a nucleophilic displacement on the oxonium ion, in which a bond between halogen and carbon begins to form while the water molecule is breaking away:

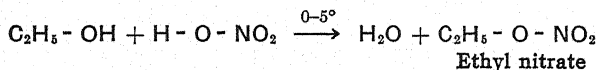


8-10 Esters are compounds formed by the elimination of water between an alcohol and an acid. The acid may be either organic or inorganic. The production of esters of organic acids, such as butyl acetate, is the largest industrial use of many alcohols:

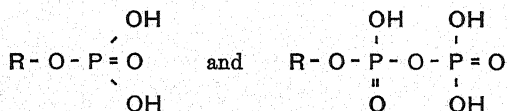


These esters are described in Chapter 12.

There are known also many esters of alcohols with inorganic acids such as nitric, nitrous, carbonic, boric, phosphoric, and sulfuric.¹ If the acid is weak (*e.g.*, carbonic acid), its esters are best obtained by an indirect method such as the reaction between an alkyl iodide and the silver salt of an acid. Strong acids esterify alcohols directly, *e.g.*,



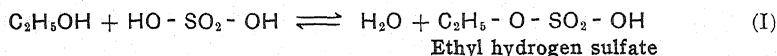
This reaction requires careful regulation to prevent oxidation of alcohol by nitric acid, and, in general, the nitric acid esters of monohydric alcohols are of minor interest. The esterification of *polyhydric* compounds (ethylene glycol, glycerol, cellulose) with nitric acid yields some of our most important explosives. Esters of *phosphoric* and *pyrophosphoric* acids of the general types



are involved in many biochemical processes (Sec. 27-9).

¹ The alkyl halides are, in effect, esters of the halogen acids.

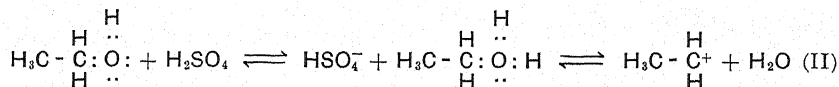
8-11 Esters of sulfuric acid are formed readily by reaction between alcohols and concentrated sulfuric acid. The most common are the *alkyl hydrogen sulfates* in which only one hydrogen atom of the acid has been replaced by a hydrocarbon group, *e.g.*,



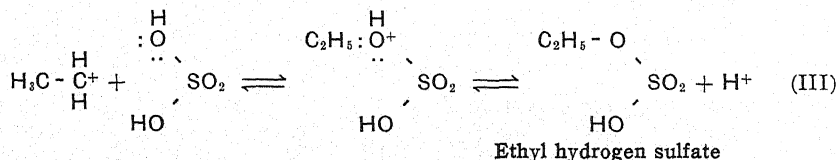
We have seen that these compounds are formed also when alkenes are absorbed in sulfuric acid [equation (V), Sec. 3-10].

Ethyl hydrogen sulfate is often called ethylsulfuric acid in recognition of the fact that, because it retains one of the well-ionized hydrogen atoms of H_2SO_4 , it is a strong acid and reacts with bases to yield salts such as $\text{C}_2\text{H}_5\text{O}.\text{SO}_3^-\text{K}^+$, potassium ethyl sulfate. Ethyl hydrogen sulfate is a syrupy liquid (*d*, 1.316) which crystallizes with difficulty, is freely soluble in water, and is seldom isolated. Much more important are the analogous esters of higher alcohols, C_{12} to C_{18} , the sodium salts of which constitute one major class of synthetic detergents (Sec. 14-7). It should be noted that equation (I), which is typical for other esters, is reversible. This means that the linkage $\text{R.O.SO}_3\text{H}$ is readily split by hydrolysis, in which respect it differs sharply from the direct sulfur-carbon linkage of the sulfonic acids, $\text{R.SO}_3\text{H}$.

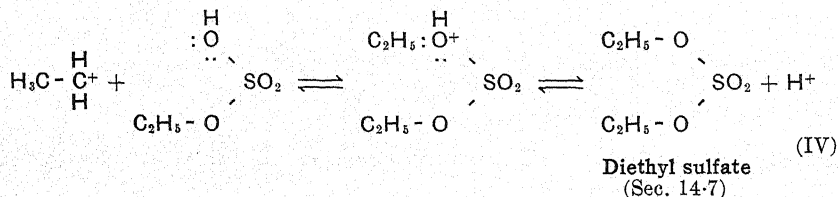
In conformity with what was stated in Section 8-8, it must be assumed that the reaction of an alcohol with sulfuric acid begins with the formation of a carbonium ion, *e.g.*,



The latter may react with sulfuric acid:

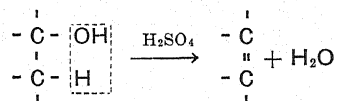


or, in similar fashion, with ethyl hydrogen sulfate:

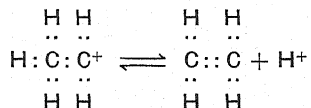


8-12 Competing Reactions; Dehydrations. The solution of an alcohol in sulfuric acid is an equilibrium mixture consisting principally of alkyl hydrogen sulfates and dialkyl sulfates. Since reactions (III) and (IV) of the preceding section are reversible, these esters serve as reservoirs of potential carbonium ions. The further reactions of these ions may yield various different products.

Dehydration of Alcohols to Alkenes. Heating an alcohol with sulfuric acid was described (Sec. 3-7) as a general laboratory method for preparing alkenes. The reaction was represented, for simplicity, by over-all equations of the general type

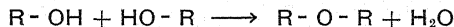


We may now describe this dehydration of an alcohol more precisely as proceeding through the formation of a carbonium ion, which stabilizes itself by expelling a proton [cf. equation (I), Sec. 7-12], *e.g.*,

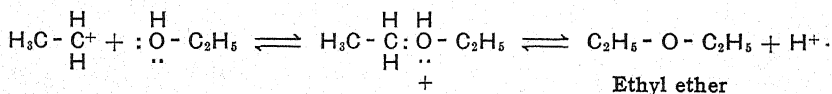


Polymers of the expected alkenes are frequently co-products when higher alcohols are dehydrated in this way because conditions are favorable for the acid-catalyzed polymerization described in Section 3-12.

Dehydration of Alcohols to Ethers. Under some conditions a molecule of water can be eliminated between two molecules of an alcohol. This forms an ether (Chap. 9), as indicated by the over-all type equation



Thus ethyl ether is formed and distills out when ethyl alcohol is dropped into a mixture of alcohol and sulfuric acid maintained at 140°C. It is regarded as formed through an attack of the electrophilic ethyl carbonium ion on an unshared electron pair of an alcohol molecule:

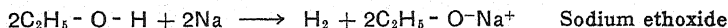


The dehydrations of alcohols to alkenes and to ethers take place under the same or similar conditions and are, therefore, competitive. With *primary* alcohols it is often possible to select a temperature and adjust the relative concentrations so that one reaction largely predominates. Thus the procedure last described gives good yields of ethyl ether at

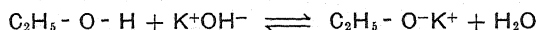
140°C, but if the temperature is raised to 165°C, ethylene is evolved rapidly. The tendency of *tertiary* alcohols to give alkenes is so strong that their ethers have to be prepared by a different method (Sec. 9-1).

The extensive production of alcohols from alkenes described in Section 8-20 is based upon another displacement of the complex equilibrium system which is set up when either an alcohol or an alkene is dissolved in sulfuric acid.

8-13 Alkoxides are saltlike electrovalent compounds formed from alcohols by reaction with an active metal, usually sodium, which displaces the OH hydrogen atom. They may be prepared by adding sodium wire or shavings to an excess of the alcohol and shaking or refluxing, *e.g.*,



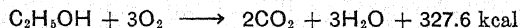
Alkoxides are also formed to some extent when a solid alkali hydroxide is dissolved in an anhydrous alcohol:



They are completely hydrolyzed, by reversal of this reaction, in water solutions. Alkoxides are used in various organic syntheses, where they act through the strongly nucleophilic ions, R.O^- , which they furnish.

The rate of reaction between sodium and anhydrous alcohols is greatest for the methyl and ethyl compounds and decreases with the increasing bulk of the hydrocarbon radicals. It is also markedly affected by the structure of the latter; *e.g.*, butanol evolves hydrogen with reasonable speed, while its isomer *tert*-butyl alcohol is so unreactive that it can be dried without appreciable loss by treatment with sodium shavings. This inertness toward sodium is understandable in terms of what has been said about the structure of tertiary alcohols (Sec. 8-7). The low $+\delta$ charge on the hydroxylated carbon increases the electron density on oxygen and gives the latter a stronger hold on the attached hydrogen atom.

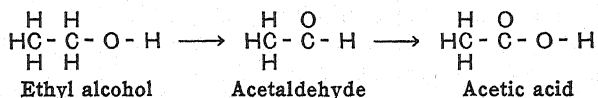
8-14 Oxidation. Alcohols burn readily like their parent hydrocarbons, *e.g.*,



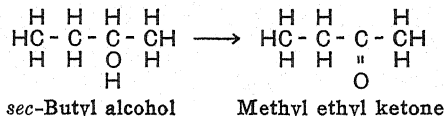
Such combustion equations summarize series of reactions in which intermediate oxidation products are formed but react further so rapidly that they are not detectable under most conditions.

Alcohols differ sharply from most saturated hydrocarbons in that they are readily oxidized by various reagents (*e.g.*, a solution of $\text{H}_2\text{Cr}_2\text{O}_7$ or of KMnO_4) and give intermediate products which can be isolated. Further oxidation occurs always at the carbon atom already partially oxidized. The products vary with the structure of the alcohol, as follows:

A *primary* alcohol, $R\cdot CH_2OH$, loses two atoms of hydrogen¹ to form an *aldehyde*, which is further oxidized to the corresponding acid, *e.g.*,



A *secondary* alcohol, $R_2CH(OH)$, similarly loses two atoms of hydrogen to form a *ketone*; the latter, containing no hydrogen on the partially oxidized carbon, is resistant to further oxidation and is ordinarily the end product obtained, *e.g.*,



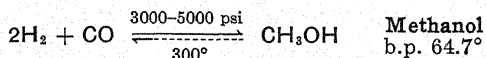
The conversion of primary and secondary alcohols into aldehydes and ketones, respectively, is considered further in Section 10·2.

Tertiary alcohols, $R_3C(OH)$, are resistant to neutral² oxidizing agents.

SOME IMPORTANT ALCOHOLS

The manufacture of alcohols is a major field of chemical industry. Specific methods used for producing a number of them are described below. Other industrial methods leading to mixtures from which individual alcohols may be isolated include: (1) the controlled oxidation of propane-butane gases (Sec. 6·19), which yields methanol and *n*-propyl alcohol among its products; (2) the complex mixture of oxygenated by-products of the Fischer-Tropsch synthesis (Sec. 6·11), a potential source of higher alcohols in large quantities; (3) reduction of aldehydes produced by the Oxo process (Sec. 10·3); (4) reduction of esters of higher acids contained in the natural fats and fatty oils (Sec. 16·22), an important source of the C_{12} , C_{14} , C_{16} , and C_{18} normal primary alcohols.

8·15 Methanol is produced in very large quantities³ by reaction between carbon monoxide and hydrogen in the presence of a suitable catalyst such as a mixture of zinc and chromium oxides:



¹ Among covalent compounds it is convenient to define oxidation as either the *loss* of hydrogen atoms or the *gain* of oxygen (cf. Sec. 10·2, paragraph 3).

² This indifference of tertiary alcohols is often obscured by the fact that, in the presence of *acids*, they are so easily dehydrated to alkenes; the latter of course are easily oxidized, with chain cleavage at the double bond. Hence, the total effect of *acid* oxidants is to convert the tertiary alcohol into a *mixture* of carboxylic acids, no one of which contains as many carbon atoms as the original alcohol.

³ Over 900 million pounds, USA, 1951.

This reaction is a variant of the Fischer-Tropsch process. The yield is about 60 per cent (without recycling). Methanol is used principally for the manufacture of formaldehyde (Sec. 10-2) and as an antifreeze. It is also the source of methyl groups in various synthetic organic chemicals such as dimethylamine and dimethylaniline. Methanol has excellent solvent powers, but this use is somewhat restricted by the fact that it is a general systemic poison and exerts a specific effect on the optic nerve, which can result in blindness.

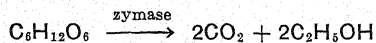
Methanol was formerly called *wood alcohol* because it was obtained as a by-product of the destructive distillation of wood.

8-16 Ethyl alcohol, *ethanol*, b.p. 78.3°C, is the most important member of its family and is the compound nearly always referred to when the word *alcohol* is used without qualification, as in *alcoholic beverage*, *alcoholic solution*, etc. Very large quantities are employed as an industrial solvent (e.g., in varnishes, perfumes, pharmaceutical preparations, the manufacture of smokeless powder) and as a radiator antifreeze. For purposes where purity is not essential it is customary to use *denatured alcohol*; this is 95 per cent ethyl alcohol to which has been added 5 to 10 per cent of foreign substances to prevent its use as a beverage. Such denatured alcohol is exempt from the high internal revenue taxes and the other restrictions imposed by most countries on pure ethyl alcohol and alcoholic beverages.

Ethyl alcohol is said to enter directly or indirectly into the preparation and manufacture of more different organic compounds than any other aliphatic substance. These include the ethyl esters of a large number of acids and many other compounds which carry the word ethyl in the name.

Ethyl alcohol is produced in the United States both from ethylene (Sec. 8-20) and by fermentation. The latter is its major source throughout the rest of the world.

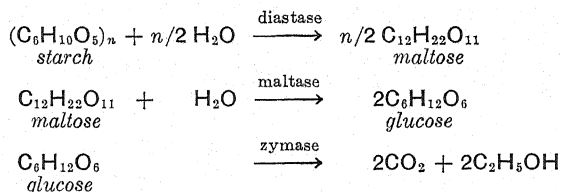
8-17 Alcohol by Fermentation. Glucose and the other six-carbon sugars that occur in nature are converted into ethyl alcohol and carbon dioxide by reactions which are catalyzed by the enzyme-complex *zymase*, supplied by brewer's yeast. The series of reactions is quite complicated (Sec. 27-9) and some by-products are formed, but the essential results of alcoholic fermentation are summarized by the over-all equation



A major source of cheap fermentable sugars in the United States is crude (*blackstrap*) molasses imported from sugar mills in the tropics.

The more important, world-wide raw material is *starch* (Sec. 18-29) as found in rice, potatoes, and cereals such as corn and rye. Starch is not fermentable by yeast *zymase* and therefore requires a preliminary treat-

ment, called saccharification or malting, through which it is hydrolyzed to malt sugar (maltose). For this purpose the finely divided, starchy raw material, such as corn meal, is cooked with steam, suspended in water at about 30°C, and treated with an extract of malt. *Malt* is sprouting barley grains; it furnishes the enzyme *diastase* which catalyzes the hydrolysis of starch. When this reaction has ended, brewer's yeast is added; this contains another enzyme, *maltase*, which hydrolyzes maltose to glucose, together with the zymase which brings about alcoholic fermentation. The sequence may be summarized as follows:



The activity of zymase is inhibited by an alcoholic content in excess of about 14 per cent; hence, this is the limiting concentration of alcohol obtainable by fermentation. To produce industrial alcohol, the dilute fermentation mixture is purified and concentrated by continuous fractional distillation in column stills. A mixture containing 95.6 per cent by weight of ethyl alcohol and 4.4 per cent of water boils constantly (at 78.15°C) and cannot be further concentrated by fractional distillation. This is the refined "95 per cent" alcohol, or *neutral spirits*, of commerce.

8-18 Absolute alcohol is ethyl alcohol containing not over 0.1 to 0.2 per cent water. It differs from ordinary 95 per cent alcohol in its much higher miscibility with hydrocarbons and other nonpolar compounds. Absolute alcohol is very hygroscopic and requires careful protection from moist air. It was formerly made in the laboratory by refluxing 95 per cent alcohol with quicklime; the latter unites chemically with water and retains it when the alcohol is distilled off. Absolute alcohol is now manufactured on a relatively large scale by the fractional distillation of mixtures of water, ethyl alcohol, and benzene. First there distills over (64.85°C) a constant-boiling mixture containing 74.1 per cent by weight of benzene, 7.4 per cent of water, and 18.5 per cent of alcohol. After the water has been removed by this operation the temperature rises to 68.24°C and a constant-boiling mixture of 67.63 per cent benzene with 32.37 per cent of alcohol comes over. When all the benzene has been removed, substantially pure anhydrous ethyl alcohol (b.p. 78.3°C) distills.

This method of adding a third substance, which forms a constant boiling mixture with one of two other substances, is widely used in making industrial separations which would otherwise be impracticable. It is called *azeotropic* distillation.

8-19 Alcoholic beverages have been known since very early times¹ because fruit juices and other dilute sugar solutions readily undergo alcoholic fermentation when left exposed to the air. Fruit skins usually carry yeast cells and, even when these

¹ "And Noah began to be an husbandman, and he planted a vineyard. And he drank of the wine, and was drunken." Gen. 9: 20-21.

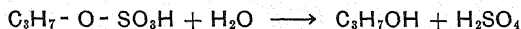
are not present or have been destroyed by boiling, their spores seem to be universally present in air that has not been carefully sterilized.

Those which have not been distilled are known as *fermented* beverages (wine, beer, ale, etc.). As already explained, their alcoholic content is limited to about 14 per cent unless alcohol is added, as such, *e.g.*, in *fortified* wines such as port and sherry. In distilled liquors (whisky, rum, brandy, gin, etc.), the alcohol is concentrated to about 50 per cent by distillation. All distilled liquors consist essentially of water and alcohol; individual flavors result from small amounts of other substances arising from the different materials subjected to fermentation.

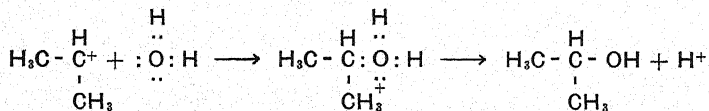
Proof. Internal-revenue taxes on alcoholic beverages are based on so-called *proof gallons* instead of the standard or wine gallons used in measuring other liquids. According to an act of Congress, a liquid containing 50 per cent alcohol by volume is defined as *proof spirit* or 100 degrees proof. Ordinary 95 per cent alcohol is, therefore, 190 degrees proof and one wine gallon equals 1.9 proof gallons.

8-20 Alcohols from Alkenes. When ethylene is passed under pressure into 90 per cent sulfuric acid maintained at about 82°C, the gas is absorbed. The acid solution is then diluted with water and live steam passed in. Dilute ethyl alcohol distills and is concentrated in a column to the usual 95 per cent product. A like procedure in which propene is absorbed in sulfuric acid yields large quantities¹ of isopropyl alcohol (b.p. 82.5°C). Smaller but still important amounts of higher alcohols (*e.g.*, *sec*-butyl, *tert*-butyl, 2-pentanol) are produced similarly from butenes, pentenes, etc. With the exception of ethyl, all the alcohols manufactured in this way are either secondary or tertiary.

The strongly acid solution in which propene, for example, has been absorbed contains isopropyl hydrogen sulfate and isopropyl sulfate. The formation of the alcohol on dilution and steam distillation is commonly represented as a direct hydrolysis of these esters, *e.g.*,



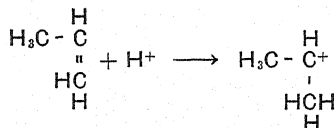
There is, however, better reason to suppose that the esters serve rather as reservoirs of carbonium ions which react with water to form the alcohol obtained:



This reaction, it will be noted, is the reverse of the one through which carbonium ions are formed by reaction between an alcohol and an acid, as expressed by equation (II), Section 8-11.

¹ The production of ethyl and isopropyl alcohols from ethylene and propene was 735 and 866 million pounds, respectively (USA, 1950). This method yields about the same amount of industrial ethyl alcohol as the fermentation process.

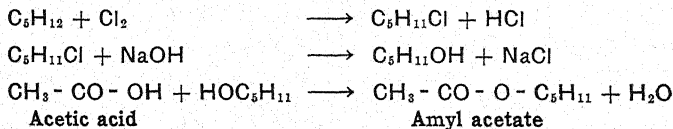
The fact that only secondary and tertiary alcohols are formed from alkenes higher than ethylene is explained by Markownikoff's rule. The proton furnished by sulfuric acid adds to that carbon atom of a double bond which has the smaller number of other carbon atoms attached. The resulting carbonium ion will therefore carry its plus charge on a secondary or a tertiary carbon atom (except in the addition to ethylene, where there is no choice), *e.g.*,



8-21 Butanol, $\text{C}_4\text{H}_9\text{OH}$, *n*-butyl alcohol, is manufactured from molasses or from cooked cornstarch by fermentation with the aid of a specific bacterium (*Clostridium saccharobutyl acetonicum liquefaciens*). The reactions are entirely different from those of ordinary "alcoholic fermentation." Carbon dioxide and hydrogen are evolved, and butanol, acetone, and ethyl alcohol are produced in the proportions of about 6:3:1. These are separated and purified by fractional distillation. In an equally important method in this country, butanol is produced from acetaldehyde through the aldol condensation (Sec. 10-9).

Butanol (b.p. 117.7°C) is used as such in lacquers but in much larger amounts for the manufacture of butyl acetate and other organic esters, which are among the most important lacquer solvents.

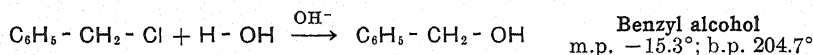
8-22 Amyl Alcohols. The major source of five-carbon alcohols is the mixture of monochlorides, $\text{C}_5\text{H}_{11}\text{Cl}$, obtained by chlorinating the pentanes (Sec. 7-5). These are hydrolyzed by heating with dilute sodium hydroxide to a mixture of the corresponding alcohols. The product, sold as Pentasol, consists essentially of five isomers, mainly 1-pentanol, 3-methyl-1-butanol, and 2-methyl-1-butanol, with smaller amounts of 3-pentanol and 2-pentanol. Pentasol is used as such in lacquers and in larger quantities after conversion into mixed amyl acetates (Pentacetate). Disregarding isomerism, the essential equations are



This process owes much of its success to the fact that the separation of individual compounds is unnecessary. The five amyl acetates in the final product all boil in the narrow range 132 to 148°C (*i.e.*, they have nearly the same rate of evaporation) and have substantially equal solvent powers.

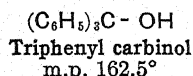
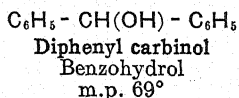
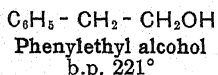
Fusel Oil. In the manufacture of ethyl alcohol by the fermentation of sugars derived from starch, small amounts of higher alcohols are formed. These boil considerably above ethyl alcohol and collect in the still tailings when the latter is refined. The *fusel oil* thus obtained is composed mainly of isoamyl alcohol (3-methyl-1-butanol) together with 2-methyl-1-butanol and isobutyl alcohol. This mixture is refined by fractional distillation. Fusel oil was formerly the only significant source of five-carbon alcohols and their derivatives. The term *amyl*, so widely used instead of *pentyl*, arose from the use of starch (L., *amylum*) as the source of the fermented sugars; actually the components of fusel oil appear to originate not in the starches but in proteins of the grain.

8-23 Aromatic Alcohols. The simplest compound of this class is *benzyl alcohol*, which is usually made by hydrolyzing benzyl chloride with steam and dilute alkali:



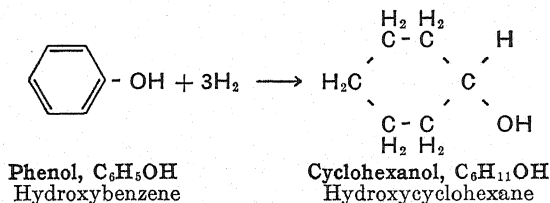
It is also obtainable from benzaldehyde, both by simple reduction and by the Cannizzaro reaction (Sec. 10-17). Benzyl alcohol is a liquid of faint and rather pleasant odor, not at all resembling that of phenol and the cresols (the latter are its isomers). Its important chemical properties are those depending on reactions of the CH_2OH group, in which it closely resembles any primary aliphatic alcohol. Thus it reacts with sodium but not with sodium hydroxide, can be dehydrated to benzyl ether, $\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{O} \cdot \text{CH}_2 \cdot \text{C}_6\text{H}_5$, reacts with acids and acid chlorides to form many benzyl esters, and is readily oxidized to benzaldehyde, $\text{C}_6\text{H}_5 \cdot \text{CHO}$, and then to benzoic acid. The hydrogen atoms attached to the nucleus are able to enter into the usual substitution reactions of benzene but, in so doing, show none of the special reactivity observed in the *ortho* and *para* hydrogen atoms of phenol.

Other aromatic alcohols of somewhat similar chemical properties include



Phenylethyl alcohol, which occurs in the oil of roses and in a few other flowers, is valuable in the perfume industry on account of its roselike odor and the odors of some of its esters. It can be made by reacting phenylmagnesium bromide with ethylene oxide, by condensing benzene with ethylene oxide in the presence of aluminum chloride, and by reducing esters of phenylacetic acid, $\text{C}_6\text{H}_5 \cdot \text{CH}_2 \cdot \text{COOH}$. *Diphenyl carbinol* is readily prepared in the laboratory by reducing benzophenone ($\text{C}_6\text{H}_5)_2\text{CO}$, or from benzaldehyde and phenylmagnesium bromide by the Grignard reaction. *Triphenyl carbinol* is prepared by the Grignard synthesis from benzophenone and phenylmagnesium bromide. As in other tertiary alcohols, the OH group is very easily replaced by Cl when the alcohol is treated with concentrated hydrochloric acid.

8-24 Alicyclic Alcohols. The most important alicyclic alcohol is *cyclohexanol*. This is manufactured by the catalytic hydrogenation of phenol in the presence of nickel; six atoms of hydrogen are added to the nucleus as in the hydrogenation of benzene:



Cyclohexanol is a viscous liquid (m.p. 23.9°C; b.p. 161.5°C; *d*, 0.962) which closely resembles in both chemical and physical properties the open-chain alcohols of about the same molecular weight. It is practically insoluble in water, and solubility is not increased by the presence of alkalis. Like other secondary alcohols it is readily oxidized to the corresponding ketone, cyclohexanone; this is its most important reaction because it is a step in one method for the production of *nylon* (Sec. 19-7). Cyclohexanol is also used as a solvent under the name Hexalin.

Several alicyclic alcohols occur in nature, *e.g.*, *menthol* or 3-hydroxymenthane (Sec. 4-3) which is a major component of oil of peppermint. Other alicyclic alcohols of much more complicated structure and great biological importance are the *sterols* (Sec. 27-18).

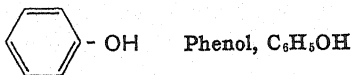
8-25 Laboratory Synthesis of Alcohols. The industrial methods for producing alcohols are more striking for their diversity than for any similarity. The most important *general reactions* used in the laboratory for preparing alcohols include: the alkaline hydrolysis of halides (Sec. 7-8), the reduction of aldehydes and ketones by addition of hydrogen to their C=O groups (Sec. 10-5), and the reduction of esters (Sec. 12-8). All these yield alcohols with carbon chains corresponding to those in the compounds used.

The *Grignard reaction* is the most important general method for synthesizing alcohols with longer chains. It utilizes the addition reactions of Grignard reagents with aldehydes and ketones (Sec. 10-6) and with ethylene oxide (Sec. 16-5).

PHENOLS

Hydroxyl derivatives of aromatic hydrocarbons in which the OH group is attached to a *nuclear* carbon atom are called phenols. These compounds may be described also as *aryl* hydroxides and are represented conveniently by the type formula Ar.OH. The family name, phenol, is the same as that of the simplest member, hydroxybenzene.

8-26 Phenol crystallizes in colorless prisms (m.p. 42 to 43°C) which often become pink on standing and have the characteristic odor of "carbolic acid." It distills without decomposition (b.p. 181.4°C) and



is readily volatile with steam. Phenol dissolves freely in ethyl alcohol, ether, benzene, and many other organic liquids. Its miscibility with water at ordinary temperatures is limited¹ but considerably exceeds that of any six-carbon monohydric alcohol. Crystals of phenol and its concentrated solutions produce painful burns on contact with the skin; dilute solutions, too weak to produce local irritation, act as a poison when taken internally.

The largest single use of phenol is in the manufacture of synthetic resins of the Bakelite type (Sec. 23-8). It is also used for making many important aromatic intermediates and finished products (Fig. 23-2), for hydrogenation to cyclohexanol, and as a disinfectant. Phenol was one of the first antiseptics used in surgery (Lister, 1867), but for this purpose it has now been largely replaced by equally effective and less irritant substitutes.

8-27 Acidity. Phenol is definitely an acid, although a very weak one ($K_a = 1.3 \times 10^{-10}$ at 25°C). In a tenth molar solution only about one molecule in 25,000 is ionized, thus giving a hydrogen-ion concentration² too low to redden methyl orange. Nevertheless, acidity and the resulting solubility in alkaline solutions have an important bearing on the isolation and manipulation³ of phenols.

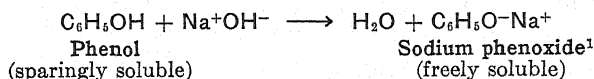
¹ At 20°C, a saturated solution of *phenol in water* contains 8.36 per cent by weight of phenol. Solubility is decreased by neutral salts and sodium chloride is commonly used in the laboratory for salting it out from aqueous solutions.

The liquid *carbolic acid* of the drugstore is a solution of *water in phenol*, prepared by melting the crystals and adding about 10 per cent of water. This lowers the melting point and prevents solidification on cooling. A saturated solution at 20°C contains 27.84 per cent by weight of water. Miscibility is increased by mutual solvents such as alcohol and glycerol and also by rise in temperature; above 68.4°C phenol and water are miscible in all proportions.

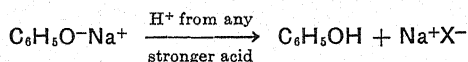
² The destructive action of "carbolic acid" on the skin and mucous membranes is not the result of its strength as an acid, in spite of popular misconceptions to the contrary. The hydrogen-ion concentration normally found in the human stomach (owing to hydrochloric acid) is at least 25,000 times as great as that which could be produced by a fatal dose of phenol.

³ In laboratory manipulations it is important to remember that free phenol (sparingly soluble in water, volatile with steam, and freely soluble in ether) cannot be present in a strongly alkaline solution; this would contain only a phenoxide (freely soluble in water, nonvolatile with steam, and insoluble in ether). In order to isolate it, phenol must be liberated by acidifying the solution.

A concentrated solution of sodium hydroxide will dissolve many times as much phenol as an equal volume of water, through the reaction



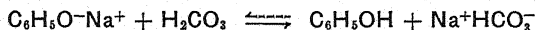
Thus phenol is extracted from coal-tar distillates by agitating them with sodium hydroxide solutions (Sec. 6-24). Phenol passes into the alkaline water layer as soluble sodium phenoxide. Then the solution is drawn off and acidified; phenol—because it is a *weak* acid—is liberated and separates as an oily layer of *crude carbohic acid*:



This may be used as such or washed, dried, and fractionally distilled to produce pure phenol.

General Test for Acidic Compounds. Greater solubility in dilute sodium hydroxide solution than in water is the most practical general test for distinguishing between organic compounds which are *acidic* and those which are neutral or basic. This test is far more reliable than the use of indicators, except with the relatively few compounds which are freely soluble in water.

Simple phenols can be differentiated from more strongly acidic compounds such as carboxylic acids (Chap. 11) by failure to dissolve in solutions of sodium bicarbonate. Because these phenols are much weaker even than carbonic acid, equilibrium in the system lies far to the right



and $\text{C}_6\text{H}_5\text{OH}$ can be liberated from a solution of sodium phenoxide by saturating with CO_2 .

8-28 Other Reactions of the OH Group. The greater acidity of phenols makes it possible to prepare phenoxides readily by the use of NaOH or KOH instead of requiring the alkali metals, as is necessary in forming alkoxides. Phenols differ further from alcohols in that the OH group *cannot* be replaced by a halogen atom through the action either of a hydrogen halide or of a phosphorus halide.

In other reactions of the OH group the two classes of compounds are quite similar. Thus phenol readily yields ethers, $\text{C}_6\text{H}_5\text{O.R}$, and many esters both of organic and inorganic acids. One of the more important of the latter is triphenyl phosphate, $(\text{C}_6\text{H}_5\text{O})_3\text{PO}$, which is an industrial plasticizer.

¹ Known also as sodium phenylate and sodium phenate.

8-29 Nuclear reactions of phenol are much more characteristic. Nuclear hydrogenation, to cyclohexanol, is easier than with benzene. The OH group also makes the nucleus easily oxidized. Thus a solution of phenol reduces alkaline permanganate solutions about as readily as does ethylene. This reaction is not useful—its products are mainly salts of aliphatic acids resulting from *ring cleavage*—and is mentioned only because it must be avoided. Special precautions against oxidation and ring cleavage are necessary whenever phenol is treated with an oxidizing agent (*e.g.*, in nitration).

Nuclear Substitutions. The hydroxyl group attached to the benzene nucleus is strongly *ortho*- and *para*-directing. It also highly activates these positions so that the hydrogen atoms are replaced with extraordinary ease in all the usual aromatic substitution reactions. This is illustrated by the following comparison with benzene:

Phenol

When a dilute aqueous solution of phenol is treated with bromine water, *three* hydrogen atoms (*o*- and *p*-) are substituted, with the immediate precipitation of 2,4,6-tribromophenol.

Relatively dilute nitric acid is able to convert phenol into 2,4,6-trinitrophenol (picric acid).

Benzene

When undiluted benzene and liquid bromine, with iron added as a catalyst, are allowed to stand at ordinary temperature, reaction is relatively slow and the main product is *mono*-bromobenzene.

The *trinitration* of benzene requires prolonged heating with a mixture of fuming nitric and sulfuric acids.

The hydrogen atom in the *para* position is especially active. In consequence, it is easily replaced in many reactions which either do not occur at all with benzene or proceed too slowly for practical use.¹

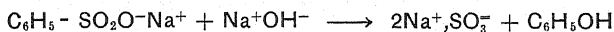
8-30 Resonance between the OH group and the aromatic nucleus explains the special reactivity of the *ortho* and *para* positions in phenol. The over-all effect is to place $-\delta$ charges on the carbon atoms in these positions (as explained more fully in Section 22-7), thus making them susceptible to attack by the electron-seeking reagents which bring about most aromatic substitutions (Sec. 22-5). Resonance likewise explains why phenols are more acidic than alcohols (Sec. 22-11).

8-31 Production of Phenol. Formerly coal tar was the principal source of phenol, but it now furnishes less than 10 per cent of the production in the United States. The remainder is made synthetically by the following methods, in each of which benzene is the starting material.

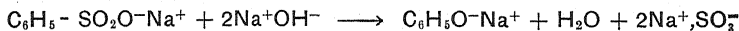
Alkali Fusion Method. Benzene is sulfonated, and the benzene-sulfonic acid is neutralized. The resulting sodium benzenesulfonate is then reacted with *fused* sodium hydroxide (m.p. 318.4°C). Under this drastic

¹ A number of these reactions are indicated in Figure 23-2 and discussed in Sections 23-8*ff*.

treatment the SO_2ONa group is replaced by OH to form phenol, and the latter is converted immediately by the excess alkali into sodium phenoxide:



Combining gives the over-all equation:



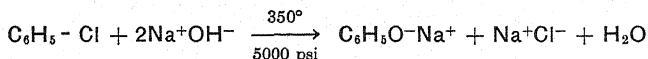
The fusion mass is run into water and the sodium sulfite filtered off. The liquid is then acidified



and the liberated phenol purified by distillation.

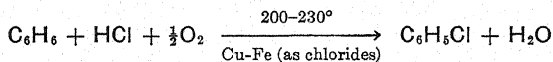
This, the classic process, has been superseded to a great extent by the other methods described below, which are less dependent upon finding a market for enormous quantities of by-products, *viz.*, sodium sulfite and sodium sulfate.

Chlorobenzene Process. Benzene is chlorinated and chlorobenzene is hydrolyzed in the liquid phase by a solution of sodium hydroxide:

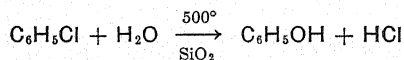


The sodium phenoxide is acidified with HCl from the chlorination step and the phenol purified by distillation. Success of the method depends to a large extent upon construction of industrial equipment capable of withstanding both the high pressure developed and the corrosive attack by sodium hydroxide at the necessary high temperatures. The role of phenyl ether, a by-product of this process, is described in Section 9-10.

Raschig Process. Chlorobenzene is formed by a vapor-phase reaction of benzene with hydrogen chloride and atmospheric oxygen:



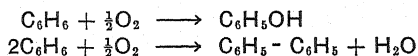
Chlorobenzene is then hydrolyzed in the vapor phase by steam:



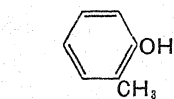
Both operations are conducted at atmospheric pressure, and the hydrogen chloride formed in the second step is recovered and used again in the first. Thus benzene and atmospheric oxygen are the only materials consumed. Only about 10 per cent conversion in each step is attained in a single pass over the catalyst, but "recycling" yields phenol equiva-

lent to 70 to 85 per cent of the benzene consumed. Phenyl ether is the principal by-product.

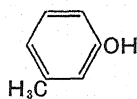
Benzene Oxidation Process. In this quite recent process, benzene vapors and air are exposed briefly to a temperature of 600 to 800°C in a firebrick reactor. Some aliphatic acids, formed through ring cleavage, are by-products, and the aromatic product is about one-fifth biphenyl:



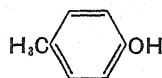
8-32 Homologues of phenol contain one OH group and one or more alkyl side chains attached to a benzene nucleus. A mixture of the three *cresols*, called *cresylic acid*, is extracted from coal-tar distillates in much the same way as phenol:



o-Cresol
m.p. 30.1°; b.p. 190.8°



m-Cresol
m.p. 10°; b.p. 202.8°

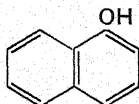


p-Cresol
m.p. 34.8°; b.p. 201.1°

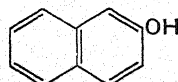
It is used for the manufacture of synthetic resins (Sec. 23-8), disinfectants, and tricresyl phosphate (a plasticizer). The cresols closely resemble phenol in odor, in chemical properties, and in their effects on micro-organisms. A mixture of cresylic acid sodium salts and soaps (Lysol) is a common disinfectant said to have about twice the germicidal power of phenol.

Higher Homologues. Some of the isomeric *xyleneols* or hydroxyxylenes occur in coal tar, and small amounts of other higher homologues are plant products found in essential oils. Among the commonest of the latter are thymol and carvacrol, which are monohydroxy derivatives of *p*-cymene. A number of higher homologues (*e.g.*, *tert*-butyl phenol) are manufactured in considerable quantities by alkylating phenol with alkenes in the presence of sulfuric acid (Sec. 23-13).

8-33 Naphthols, $\text{C}_{10}\text{H}_7\text{OH}$, are the hydroxyl derivatives of naphthalene:



1-Naphthol
 α -Naphthol
m.p. 96°



2-Naphthol
 β -Naphthol
m.p. 122°

Both are colorless solids when freshly prepared but gradually darken; their odors are fainter than those of the simpler phenols. They are freely soluble in ether and most other organic solvents. Solubility in

water is very limited but is somewhat increased by alkalis, thus indicating faintly acidic properties. Chemically, they resemble phenol and the cresols. β -Naphthol, which is much the more important, is manufactured in large quantities by alkali fusion of sodium 2-naphthalenesulfonate. It is used mainly for the production of azo dyes and of antioxidants for rubber.

8-34 Laboratory Preparation of Phenols. The most general method for making compounds in which an OH group is attached to an aromatic nucleus is alkali fusion of the corresponding sodium sulfonates ($\text{Ar}.\text{SO}_3\text{Na} \rightarrow \text{Ar}.\text{OH}$). With mixed compounds, however, this method is often limited by the fact that—under its drastic conditions—other groups also may be removed from the molecule. An alternate method which often proves useful consists in nitration, followed by reduction of $\text{Ar}.\text{NO}_2$ to $\text{Ar}.\text{NH}_2$, and replacement of NH_2 by OH through the diazo reaction (Sec. 13-17).

Replacement of chlorine by hydroxyl is *not* a practical laboratory method for making simple phenols because the necessary high-pressure equipment is not available. But the halogen atom in certain substituted aryl halides (*e.g.*, 2,4-dinitrochlorobenzene) is much more reactive and can be replaced by heating with alkaline solutions under laboratory conditions (Sec. 22-13).

DETECTION AND IDENTIFICATION

8-35 Alcohols are *neutral* compounds. They evolve hydrogen when treated with sodium shavings. Failure to give this test excludes most alcohols, but a positive response is significant only in the proved absence of water.

Reaction with acetyl chloride is a more reliable positive test for alcohols:

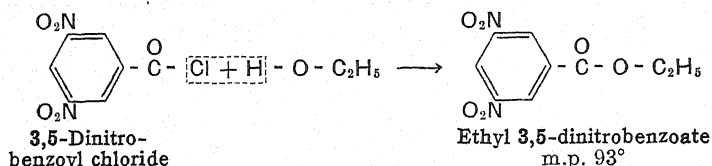


Evidences of reaction are the liberation of hydrogen chloride and the evolution of heat (both of which occur likewise when acetyl chloride is added to water), accompanied by the formation of an ester. The esters are more insoluble in water than their parent alcohols and may be recognized, as a class, by their marked agreeable odors (best observed after neutralizing the test mixture with sodium carbonate). Tertiary alcohols do not yield esters by this method.

Lucas Test. Primary, secondary, and tertiary alcohols of not too high molecular weight can be differentiated through the rates with which they are converted into chlorides by treatment with the Lucas reagent (a cold saturated solution of anhydrous zinc chloride in concentrated hydrochloric acid). Alcohols below C_6 are soluble in this reagent. Tertiary alcohols react rapidly to form the corresponding insoluble chlorides; hence, clouding or milkiness may be observed at the time of mixing. Secondary alcohols cloud within 5 minutes. Primary alcohols remain clear because chloride formation is so extremely slow. Tertiary alcohols also react within a few minutes with concentrated hydrochloric acid, even in the absence of zinc chloride, while solutions of secondary alcohols in concentrated hydrochloric acid remain clear.

The *haloform reaction* (Sec. 15-10) is also useful in differentiating between certain alcohols.

Derivatives. Many alcohols can be identified by conversion to crystalline esters of 3,5-dinitrobenzoic acid, *e.g.*,



some of the higher monohydric alcohols and polyhydric alcohols such as glycerol give solid esters of benzoic acid. These are prepared by reaction with benzoyl chloride (Schotten-Baumann reaction, Sec. 12-10). Urethans (Sec. 19-10) are also excellent derivatives for primary and secondary alcohols, provided the specimens are free from water.

8-36 Phenols. An organic compound which is more soluble in dilute NaOH than in water, but which does not dissolve in NaHCO₃ solution, is probably a phenol. This inference is confirmed if both of the following tests are positive:

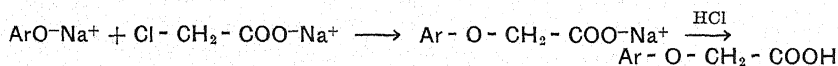
Bromine-water Test. A solution of the substance in water or in dilute ethanol is treated with bromine water until the color of bromine persists. Many phenols yield insoluble bromine substitution products which precipitate quickly.

Ferric Chloride Test. Most phenols give intense colorations—which may be red, purple, green, or black—when their solutions in water or in dilute ethanol are treated with a little ferric chloride solution. The deep purple reaction product of ordinary phenol is the anion



which is formed by coordination of one Fe⁺⁺⁺ and six C₆H₅O⁻ ions. Since these complexes are decomposed by acids, the ferric chloride reagent should be as nearly neutral as possible.

Derivatives. By taking advantage of the high reactivity of the nuclear hydrogen atoms, many phenols are easily converted into crystalline bromine and nitro substitution products. Other types of derivatives commonly prepared are urethans (Sec. 19-10), ethers, and esters. The most useful ethers are obtained by reaction between a phenoxide and the sodium salt of chloroacetic acid:



These products are known as *aryloxyacetic acids*. Phenols are esterified like alcohols, by reaction with an acid chloride in pyridine. The acid chlorides commonly used for this purpose are those of benzoic, *p*-nitrobenzoic, 3,5-dinitrobenzoic, and *p*-bromobenzenesulfonic acids.

Questions

1. (a) Summarize two lines of evidence for the hydroxyl structure of ethyl alcohol. (b) Do you see further proof in the fact that ethyl alcohol, C₂H₅O, reacts with HBr to form C₂H₅Br? Explain.

2. Explain in detail how the aliphatic monohydric alcohols satisfy the requirements of a homologous series.

3. (a) Write the structural formulas of the eight isomeric amyl alcohols, $C_5H_{11}OH$. (b) Give the systematic name of each, regarding the OH group as the principal function. (c) Name each as a carbinol. (d) Indicate which are *primary*, *secondary*, and *tertiary* alcohols.

4. Discuss the structure and properties of methanol in terms of their relations to the structure and properties of methane and water.

5. In terms of molecular association and hydrogen bonding explain: (a) why the boiling point of methanol is around 225 degrees higher than that of methane; (b) why the difference between the boiling point of an alcohol and its parent alkane decreases on ascending the series (Fig. 8-1); (c) why, in contrast with the parent hydrocarbons, the lower alcohols are freely soluble in water; (d) why the higher alcohols are better solvents for gasoline than are methyl and ethyl alcohols, even when these are anhydrous.

6. (a) How could you most readily distinguish between a saturated solution of butanol in water and a saturated solution of water in butanol? (b) Given a mixture prepared by shaking 100 ml of butanol with five times its volume of water, describe the procedures you would follow in order to recover the maximum amount of pure anhydrous butanol.

7. Absolute ethyl alcohol is miscible with gasoline hydrocarbons and is used in some tropical countries as a component of motor fuel. Predict what should happen if a pint of water were added to a gallon of such motor fuel; explain fully.

8. Write structural equations for the over-all reactions between *n*-butyl alcohol and: (a) sodium; (b) hydrogen bromide; (c) PI_3 .

9. Explain why *tertiary* alcohols: (a) yield halides with exceptional ease by reaction with concentrated water solutions of the hydrogen halides; (b) react extremely slowly with sodium.

10. (a) What is an ester? (b) Write structural formulas of the possible ethyl esters of carbonic acid, H_2CO_3 , and orthoboric acid, H_3BO_3 . (c) Explain why the alkyl halides may be considered esters of the halogen acids.

11. Construct a chart, centering about the carbonium ion $^+C_2H_5$, which shows in detail the equations for the reversible reactions connecting ethylene, ethyl alcohol, and ethyl hydrogen sulfate. (Save this chart for future additions.)

12. Show all the four-carbon compounds that might be formed by oxidation of the four butyl alcohols.

13. Show how 2-pentanol might lose water to form an ether and two alkenes. Which of the latter would predominate? (Cf. Sec. 3-7.)

14. Write over-all equations for the reactions (one or more) involved in the manufacture of: (a) methanol from coke; (b) ethyl alcohol by the fermentation of glucose, $C_6H_{12}O_6$; (c) isopropyl alcohol from propane; (d) amyl alcohols from the pentanes; (e) benzyl alcohol from toluene; (f) cyclohexanol from benzene.

15. What is "absolute" alcohol? Denatured alcohol? How many proof gallons in a barrel (42 wine gallons) of dilute ethyl alcohol 70 per cent by volume?

16. Account accurately for the fact that the alcohols, except C_2H_5OH , obtainable in good yields from alkenes are always either secondary or tertiary.

17. Point out any error or errors in the following statement: Depending upon the conditions, cornstarch can be fermented by brewer's yeast to yield mainly ethyl alcohol or mainly butanol.

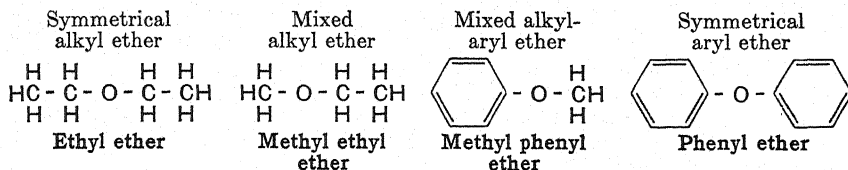
18. Explain clearly: (a) why phenol is more soluble in solutions of alkali hydroxides than in water; (b) how it can be separated from such solutions; (c) the evidence that phenol is a weaker acid than carbonic.

19. Write structural equations for the conversion of phenol into: (a) sodium phenoxide; (b) phenyl ether; (c) cyclohexanol; (d) picric acid.
20. Give specific evidence in support of the statement that the *ortho* and *para* hydrogen atoms in phenol are more reactive than hydrogen in benzene.
21. Outline a procedure, not based on fractional distillation, for the separation of phenol and benzyl alcohol so as to obtain both compounds in pure condition.
22. Write equations for all the reactions involved in the manufacture of synthetic phenol by three processes, giving the necessary conditions for each.
23. What is the relationship between benzyl alcohol and the three cresols? Describe the observations in three quick tests by means of which you could distinguish benzyl alcohol or cyclohexanol from a mixture of cresols.
24. Predict what would happen if: (a) *p*-cresol is refluxed with an active oxidizing agent with the object of preparing *p*-hydroxybenzoic acid? (b) Saligenin, *o*-hydroxybenzyl alcohol, is heated with the $\text{HBr} - \text{H}_2\text{SO}_4$ mixture commonly used for preparing alkyl bromides.
25. Write structural equations and specify necessary conditions for the manufacture of β -naphthol from naphthalene.

CHAPTER 9

ETHERS

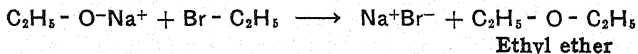
Organic compounds in which two hydrocarbon radicals are joined through an atom of oxygen are known as *ethers*. The type formula is $R.O.R'$, in which R and R' may represent any two hydrocarbon radicals, the same or different. The following structural formulas illustrate the different classes:



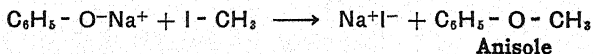
The symmetrical ethers, which contain two identical radicals, are usually named by adding the word *ether* to the name of the hydrocarbon radical, sometimes with, but oftener without, the prefix *di*-; thus $(\text{C}_2\text{H}_5)_2\text{O}$ is called ethyl ether or diethyl ether. For mixed ethers, the names of both radicals are used, that of the smaller being given first.

The two general methods for joining hydrocarbon radicals through an oxygen atom—that is, methods for the formation of ethers—are the Williamson synthesis and the dehydration of alcohols and phenols.

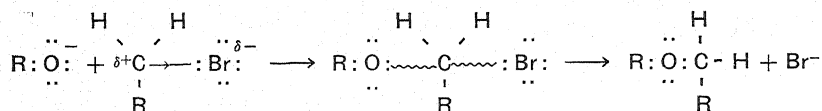
9.1 Williamson Synthesis. When ethyl bromide is heated under reflux with an alcoholic solution of sodium ethoxide, ethyl ether is formed:



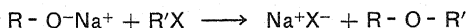
In like manner methyl iodide and sodium phenoxide give methyl phenyl ether, *anisole*:



These reactions are nucleophilic displacements (Sec. 7.10) in which the driving force is the attack of an alkoxide or phenoxide ion on the $+\delta$ carbon of an alkyl halide:

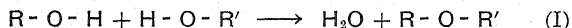


The type equation for the Williamson synthesis is



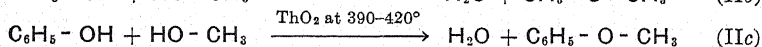
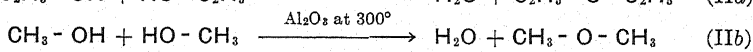
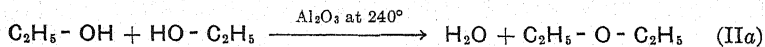
in which RO-Na^+ may stand for any alkoxide or phenoxide and $\text{R}'\text{X}$ usually represents an *alkyl* halide. Unsubstituted aryl halides like chlorobenzene require temperatures higher than those ordinarily obtainable in the laboratory. Dimethyl sulfate and diethyl sulfate (Sec. 14·7) are often used instead of the corresponding halides.

9·2 Ethers by Dehydration. Ethers can be prepared also by the elimination of water between two alcoholic or phenolic hydroxyl groups, in the sense of the type equation

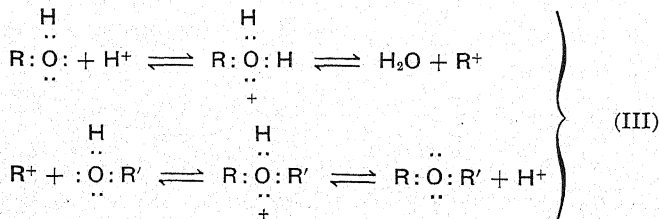


This method is limited, for the most part, to phenols and *primary* alcohols; with secondary and tertiary alcohols, dehydration to alkenes occurs too readily under the same conditions.

In the *vapor-phase* method the vapors of the alcohol or phenol, or a suitable mixture of two such compounds, is passed over a metallic oxide catalyst maintained at the required temperature, *e.g.*,



The alternate method for preparing ethers by dehydration consists in heating an alcohol, or a mixture of two alcohols, with an acid—usually, but not necessarily, sulfuric acid:



(Compare Sections 8·8 and 8·12.)

9-3 Ethyl ether, $C_2H_5.O.C_2H_5$, is the substance commonly referred to as *ether* in the laboratory, in industry, and in the operating room. It is a very volatile liquid (b.p. $34.6^\circ C$; d , 0.714), and its vapors, which are heavier than air, are highly inflammable. This combination of properties demands special precautions in its use. Ether produces anesthesia with a minimum of danger and is the most widely used general anesthetic. It is also used industrially and in the laboratory as a solvent for fats, fatty oils, and many other substances. Ethyl ether is produced mainly as a by-product of the manufacture of ethyl alcohol from ethylene.

Grignard Ether. Ethyl ether and water are somewhat miscible, and the commercial product ordinarily contains some water and 3 to 4 per cent of ethyl alcohol. The *anhydrous ether* required in the Grignard synthesis and for some other laboratory purposes is prepared as follows. Alcohol is removed by shaking commercial ether with a saturated sodium chloride solution, after which it is dried by standing with anhydrous calcium chloride and, finally, by adding sodium wire or shavings. When hydrogen is no longer evolved, anhydrous ether is distilled off, with precautions against contact with moist air. Ethyl ether may be replaced in the Grignard reaction, if desired, by one of its higher boiling homologues or by dioxane.

Ether Extractions. When shaken with water to equilibrium at $20^\circ C$, 100 grams of the water layer contains 6.9 grams of dissolved ether and 100 grams of the ether layer contains 1.3 grams of dissolved water. This mutual solubility must be kept in mind when, as often happens, ether is used to extract an organic compound from a solution of the latter in water. When a large volume of solution is to be extracted, it is customary to saturate it with sodium chloride; this reduces the solubility of ether in the solution to about 0.3 per cent. The ether layer is then separated, and the water that it contains in solution is removed by drying with calcium chloride or other suitable desiccating agent. Ether is also used in analytical chemistry for extracting fats and oils from dried milk, cottonseed meal, and similar products. For this purpose it is customary to employ anhydrous ether and some form of continuous-extraction apparatus.

9-4 Homologous Alkyl Ethers. Other symmetrical alkyl ethers are related to alcohols as is ethyl ether to ethanol. The formulas and boiling points of some of them follow:

Name	Formula	Boiling point, $^\circ C$
Methyl ether.	$CH_3.O.CH_3$	-24.9
Ethyl ether.	$C_2H_5.O.C_2H_5$	34.6
Propyl ether.	$CH_3.CH_2.CH_2.O.CH_2.CH_2.CH_3$	90.5
Isopropyl ether.	$(CH_3)_2CH.O.CH(CH_3)_2$	68.5
<i>n</i> -Butyl ether.	$C_4H_9.O.C_4H_9$	142.4
<i>n</i> -Amyl ether	$C_5H_{11}.O.C_5H_{11}$	187.5

Isomerism. With four or more carbon atoms in the molecule, isomeric alkyl ethers are possible. For example, all three of the following com-

pounds have the molecular formula $C_4H_{10}O$:

$CH_3 - O - CH_2 - CH_2 - CH_3$
Methyl propyl ether
b.p. 38.9°

$C_2H_5 - O - C_2H_5$
Ethyl ether
b.p. 34.6°

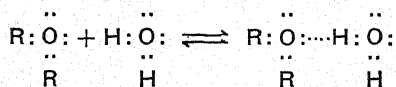
$CH_3 - O - CH(CH_3)_2$
Methyl isopropyl ether
b.p. 32.5°

For ethers of the formula $C_5H_{12}O$ it is possible to predict the existence of six isomers by considering the fact that the 5 carbon and 12 hydrogen atoms may be represented by: (1) an ethyl and a propyl radical; (2) an ethyl and an isopropyl radical; (3) a methyl radical and any one of the four butyl radicals. The alkyl ethers are isomeric also with the saturated monohydric alcohols containing the same numbers of carbon atoms. Thus, methyl ether is the isomer of ethanol and the three ethers shown above are isomeric with the four butyl alcohols.

Physical Properties. The boiling points of ethers are much lower than those of the alcohols with which they are isomeric and are close to those of hydrocarbons of about the same molecular weight, *e.g.*,

Substance	Formula	Molecular weight	Boiling point, °C
Propane.....	$CH_3.CH_2.CH_3$	44	-42.1
Methyl ether.....	$CH_3.O.CH_3$	46	-24.9
Ethyl alcohol.....	$CH_3.CH_2.OH$	46	78.3
Pentane.....	$CH_3.CH_2.CH_2.CH_2.CH_3$	72	36.1
Ethyl ether.....	$CH_3.CH_2.O.CH_2.CH_3$	74	34.6
Butanol.....	$CH_3.CH_2.CH_2.CH_2.OH$	74	117.7

This indicates that ethers are not associated liquids (Sec. 8-4). Hydrogen bonding between two ether molecules cannot take place because all the hydrogen atoms present are attached to carbon, which is not sufficiently electronegative. But ethers can, and do, form hydrogen bonds with water and other compounds containing the OH group, *e.g.*,



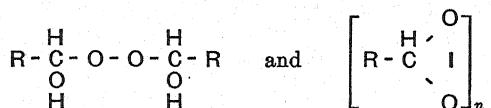
Mutual attractions arising in this way explain the partial miscibility of water and ethyl ether, which is comparable to that of butanol and water. These attractions become more important in compounds containing more than one ether linkage; many of these are completely miscible with water (*e.g.*, dioxane and the polyethylene glycols, Sec. 16-6).

Uses of Ethers. The chief use of the alkyl ethers depends on their solvent powers for fats and similar organic compounds. For a long time ethyl ether was the only one of importance for this purpose, but isopropyl

ether and butyl ether are now available in industrial quantities. These have the advantages of higher boiling points (meaning less loss in handling and less danger of fire) and practical insolubility in water.

Chemical Properties. Ethers are among the least reactive organic compounds, approaching saturated hydrocarbons in this respect. Hence they are seldom used, except as inert *solvents*, in preparing other substances. The only reactions of interest are the following.

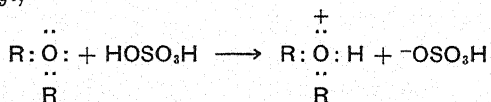
9-5 Ether Peroxides. The ethers are indifferent to the common laboratory oxidizing agents, but on standing in the presence of air (*e.g.*, in partially filled bottles) they take up oxygen to form unstable peroxides. These are mixtures which contain, among other things, compounds of the types



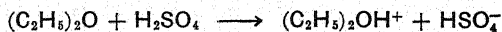
They are sensitive to heat, and dangerous explosions have resulted from distilling ethers containing them.

To *test* for the presence of peroxides, the ether is shaken with an acid solution of potassium iodide; if a peroxide is present, the brown color of free iodine will be observed. In order to *remove* peroxides, the ether is shaken with a reducing agent such as ferrous sulfate, stannous chloride, or sodium bisulfite. Danger can be avoided also by distilling over solid potassium hydroxide or metallic sodium. *Metals* inhibit peroxide formation, and iron wire may be added for this purpose to ether stored in glass bottles.

9-6 Solubility in Acids. Ethers differ from saturated hydrocarbons and organic halides by dissolving in cold concentrated acids, such as H_2SO_4 and HCl , and separating unchanged when the acid is diluted without warming, as by pouring upon crushed ice. This is due to the formation of well-ionized¹ oxonium salts which are soluble in the concentrated acids, *e.g.*,

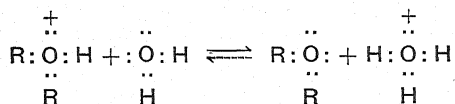


¹The following observation affords direct evidence of ionization. When ethyl ether is dissolved in 100 per cent sulfuric acid, the freezing point of the latter is lowered nearly twice as much as expected from the number of molecules dissolved. Freezing point lowering is directly proportional to the total number of dissolved particles—either molecules or ions. The reaction



gives two ions for each dissolved molecule.

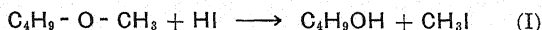
In this formation of oxonium ions, ethers act as bases, *i.e.*, as proton acceptors. Separation on dilution of the acid shows that they are weaker bases than water, with equilibrium far to the right in the system:



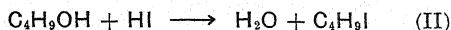
Ethers may not separate on dilution if their solutions in H_2SO_4 have been heated or allowed to stand a long time. Under these conditions the equilibrium shown in equation (III) of Section 9-2 is displaced toward the formation of carbonium ions, which may yield either water-soluble alkyl hydrogen sulfates (Sec. 8-11) or insoluble alkenes (Sec. 8-12).

The ability to dissolve in mineral acids through formation of oxonium ions is not confined to ethers and alcohols (Sec. 8-8). This property is common to most organic compounds containing oxygen—aldehydes, ketones, esters, carboxylic acids, nitro compounds, etc. Concentrated sulfuric acid (95 per cent by weight) and syrupy phosphoric acid (85 per cent) are more effective solvents than concentrated hydrochloric acid (39 per cent) because of their lower content of water.

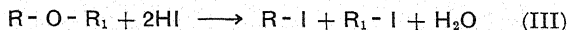
9-7 Cleavage of Ethers. A concentrated solution of hydrogen iodide (hydriodic acid) is the most widely used reagent for cleaving the C—O—C linkage in ethers. One equivalent of the acid, reacting slowly at room temperature, gives an alkyl iodide and an alcohol, *e.g.*,



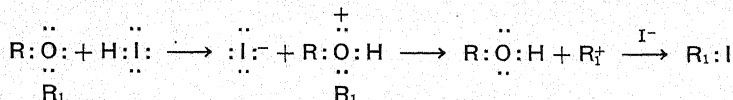
With an unsymmetrical methyl ether like this, the *methyl group* is the one which appears as the iodide. Under the more usual condition of heating with an excess of reagent, the alcohol formed in the first step is also converted to iodide:



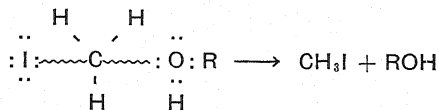
The over-all reaction under these conditions is then expressed by the type equation



Following the formation of oxonium ions by reaction with HI, ether cleavage may occur in either of the following ways. A carbonium ion (R^+ or R_1^+) may separate and then react with iodide; this sequence would be

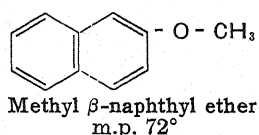
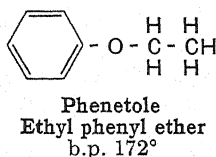
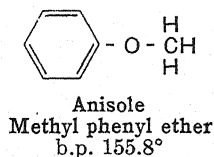


Alternatively, iodide ion may attack R or R₁ in the oxonium ion through a rearward approach, forming a new bond as a molecule of alcohol is breaking away:



Concentrated solutions of hydrogen chloride and hydrogen bromide cleave ethers as hydriodic acid does, but much more slowly. Heating with concentrated sulfuric acid or with phosphorus pentachloride is sometimes effective. It is important to note that *the ether linkage is not hydrolyzed by alkaline solutions* (distinction from esters and acid anhydrides, Chap. 12).

9-8 Alkyl-Aryl Mixed Ethers. The most important aromatic ethers are mixed compounds which may be regarded as derived from phenols by replacing the hydroxyl hydrogen atom by an alkyl radical. These include



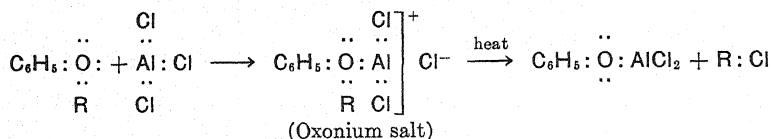
Such methyl and ethyl ethers are best prepared by dissolving the phenol in sodium hydroxide and heating with dimethyl or diethyl sulfate. Derivatives of anisole and phenetole are important dyestuff intermediates. Methyl β-naphthyl ether, *yara yara*, is used in the perfume industry as a substitute for orange-flower oil.

The *ortho* and *para* hydrogen atoms in a phenolic ether can be replaced by sulfonation, nitration, and halogenation as in the parent phenols. The carbon-oxygen linkage is even less reactive than in the dialkyl ethers but may be split by hot concentrated hydriodic acid to give one molecule of alkyl iodide and one of phenol, *e.g.*,

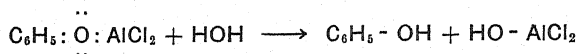


This reaction is the basis of the Zeisel method for determining the number of *methoxyl* groups, OCH₃, present in a substance of unknown structure, as follows. A weighed amount of the compound is heated with an excess of concentrated hydriodic acid; the easily volatile methyl iodide formed is distilled off and collected in an alcoholic solution of silver nitrate; CH₃I reacts with the latter, precipitating silver iodide, which is collected and weighed.

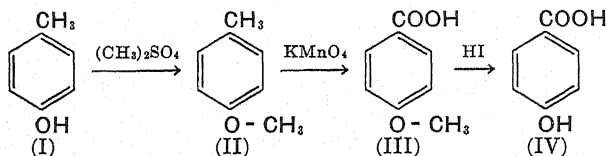
Another method effective for ether cleavage consists in heating with anhydrous AlCl₃; *e.g.*,



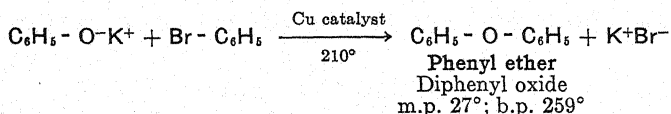
Addition of water yields the free phenol:



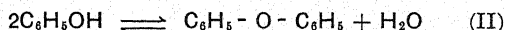
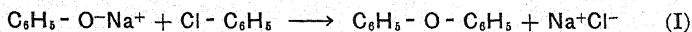
9.9 "Protection" of Phenols. Phenols are often converted into their methyl ethers for the purpose of *protecting* or masking the hydroxyl group during some laboratory manipulation. For example, the attempt to convert (I) directly into (IV) by oxidation of the methyl side chain would fail completely because oxidation—and destruction—of the aryl nucleus would prevail. This can be accomplished, however, through the reaction sequence:



9.10 Phenyl ether is the best known diaryl ether. It can be made in the laboratory by the reaction



Phenyl ether is obtained industrially as a by-product of the manufacture of phenol from chlorobenzene (Sec. 8.31). Under the conditions of this operation about 10 per cent of a charge of chlorobenzene is converted into phenyl ether through the reactions



Excess formation of ether is retarded by taking advantage of the fact that reaction (II) is reversible. The phenyl ether formed in one charge is separated and returned to the system in the next. This forces (II) to the left, in accordance with the law of chemical equilibrium, and thereby helps dispose of ether formed in the irreversible reaction (I).

Phenyl ether is used mainly as a medium for indirect heating operations which must be conducted at relatively high but constant tempera-

tures (e.g., the distillation of lubricating oils and the phenol synthesis itself). This use depends upon its high boiling point and its stability at even higher temperatures. The industrial product sold as Dowtherm A is such a medium for indirect heating. This is a mixture of 73.5 per cent phenyl ether and 26.5 per cent biphenyl, $C_6H_5.C_6H_5$, which remains fluid down to $12^\circ C$ (pure phenyl ether solidifies at $27^\circ C$) and can be heated unchanged to around $400^\circ C$ under a pressure of 10 atmospheres.

Chemical Properties. The C—O—C linkage in diaryl ethers is even more stable than in the types of ethers described above and is highly resistant to cleavage by any laboratory reagent. The diaryl ethers also differ from others in that they do not dissolve in cold sulfuric acid. This means that the unshared electron pairs on the oxygen atom are less available for union with protons to form oxonium ions.

9-11 Detection and Identification. Those ethers which contain no other functional group are found, in any system of analysis, among the neutral compounds. They are usually recognized by *eliminating* all more reactive types of oxygen compounds and *then* distinguishing from saturated hydrocarbons by solubility in cold sulfuric acid (diaryl ethers are exceptions). Final identification is usually based upon close agreement of at least two physical constants (e.g., boiling point and density) with recorded values.

Derivatives. When some of the lower symmetrical alkyl ethers are heated with zinc chloride and 3,5-dinitrobenzoyl chloride, they are converted into the 3,5-dinitrobenzoates of their parent alcohols (Sec. 8-35). Some aryl ethers yield crystalline nitro derivatives or bromine substitution products like their parent phenols. In general, suitable derivatives are hard to obtain unless the molecule also contains some functional group more reactive than the ether linkage.

Questions

1. Starting with any desired alcohols, phenols, and inorganic reagents, write all equations for the preparation of the following ethers by the Williamson synthesis: (a) methyl ether; (b) ethyl isopropyl ether; (c) propyl phenyl ether; (d) benzyl ether.
2. (a) Explain why diaryl ethers cannot be prepared, ordinarily, by the Williamson synthesis. (b) Write equations for the formation of phenyl ether as a by-product in the manufacture of phenol and account for this exception to the general rule.
3. Tertiary amyl alcohol, passed over alumina at $380^\circ C$, yields substantially no ether but a mixture of two hydrocarbons. Explain, and show the probable formulas of these hydrocarbons.
4. Sodium produces an evolution of hydrogen when the metal is added to ordinary laboratory ether; how do you reconcile this fact with the statement that ether does not react with sodium? (Give two explanations.) What is absolute ether and how can it be obtained from ordinary ether?
5. What is meant by the term "petroleum ether"? How does the material so named differ from the ethers considered in this chapter?
6. On account of its very low density ethyl ether nearly always separates as the top layer when used to extract organic compounds from water solutions. Under what conditions might the ethereal layer sink to the bottom?

7. Explain accurately: (a) the solubility of most ethers in cold sulfuric acid and the fact that they separate when these solutions are diluted without heating; (b) why nothing may separate if the solution of an ether in sulfuric acid is heated before being diluted.

8. Add the manufacture of ethyl ether from ethylene to the chart which you prepared in question 11, Chapter 8.

9. (a) Outline a simple procedure by means of which it would be possible to separate a mixture of equal parts of hexane (b.p. 69°C) and isopropyl ether (b.p. 68.5°C) so that both compounds could be obtained in a state of purity. (b) Do the same for a mixture of isopropyl ether and *n*-propyl bromide (b.p. 70.9°C).

10. What ethers are isomeric with the following compounds: (a) the butyl alcohols; (b) benzyl alcohol; (c) phenylethyl alcohol; (d) *p*-cresol?

11. Predict the number of possible ethers of the formula $\text{C}_6\text{H}_{14}\text{O}$ from the fact that there are known one methyl, one ethyl, two propyl, four butyl, and eight amyl alcohols. Explain the basis of your calculation.

12. What products, if any, would be formed by the action of an excess of hydriodic acid when heated with the following compounds: (a) ethyl isopropyl ether; (b) methyl phenyl ether (anisole); (c) ethyl benzyl ether; (d) phenyl ether.

13. Isopropyl ether has become a commercial product. (a) Connect this fact with the availability of propene. (b) Predict its solubility relations as compared with ethyl ether. (c) Suggest several advantages over ethyl ether as an industrial solvent.

14. Which of the following reactions should give a better yield of anisole and why: (a) $\text{C}_6\text{H}_5\text{ONa} + \text{CH}_3\text{Br}$; (b) $\text{C}_6\text{H}_5\text{Br} + \text{CH}_3\text{ONa}$?

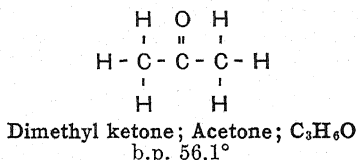
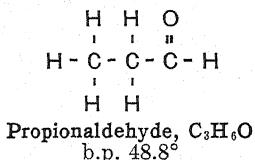
15. Write the structural formulas of the following ethers used in the perfume trade: benzyl ether, phenyl ether, methyl β -naphthyl ether, methyl *p*-cresyl ether.

16. Analysis of a certain substance shows the formula $\text{C}_4\text{H}_{10}\text{O}$. Is the compound, necessarily an ether? Show the structures of all the compounds of this formula which, on boiling with concentrated hydriodic acid, could yield: (a) $\text{C}_2\text{H}_5\text{I}$; (b) $\text{C}_4\text{H}_9\text{I}$; (c) $\text{C}_3\text{H}_7\text{I}$.

CHAPTER 10

CARBONYL COMPOUNDS; ALDEHYDES AND KETONES

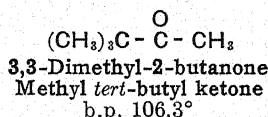
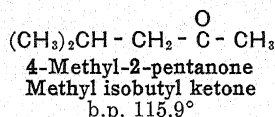
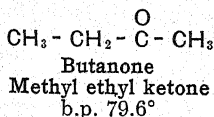
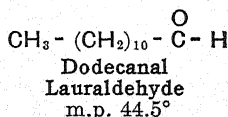
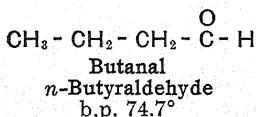
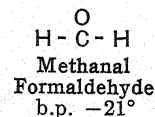
Aldehydes and ketones are hydrocarbon derivatives which contain the carbonyl group, $C=O$. If the oxygen is attached to a *primary* carbon atom the compound is an aldehyde, if attached to a *secondary* carbon atom it is a ketone, *e.g.*,



Most of the reactions of aldehydes and of ketones are those of the carbonyl group; hence, the compounds of both classes resemble each other in many chemical properties. The major differences may be ascribed to the hydrogen atom which is attached to the carbonyl carbon atom in every aldehyde but which is lacking in the ketones.

10.1 Aliphatic aldehydes and ketones containing a single carbonyl group form two homologous series, each with the general formula $C_nH_{2n}O$. Corresponding members are position isomers, as illustrated above by propionaldehyde and acetone. The most important individual compounds are formaldehyde, acetaldehyde, and acetone, each of which is described later in this chapter.

Nomenclature. The systematic names are derived from those of the parent alkanes by dropping the terminal *-e* and adding *-al* for an aldehyde and *-one* for a ketone, with the usual numbering when necessary. The first name given for each of the following compounds illustrates this system:



The more common members of both series are usually called by names derived from older systems, as follows: An aldehyde is named from the *corresponding acid* (Table 11.1) by dropping the terminal *-ic* and adding the word aldehyde, *e.g.*,

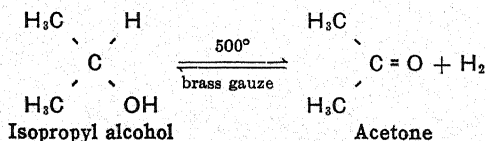


Ketones are named by adding the word ketone to the names of the two hydrocarbon radicals which are joined to the carbonyl carbon atom. This usage is illustrated above and by such names as diethyl ketone. Dimethyl ketone is universally called *acetone*.

General Properties. As in other homologous series, physical properties shift gradually and more or less regularly with increasing molecular weight. Isomeric aldehydes and ketones do not differ widely from each other in their physical constants. Both types have boiling points much closer to those of their parent hydrocarbons than to the corresponding alcohols, thus indicating that they are not associated liquids. Formaldehyde, acetaldehyde, and acetone are freely soluble in water, but this property practically disappears when there are as many as five carbon atoms in the molecule. The higher members are no more soluble in dilute acids and alkalis than in water; that is, the aldehydes and ketones are *neutral* compounds. All are freely miscible with ether and most other organic liquids. Acetone and other lower ketones have remarkable solvent powers for many widely differing types of organic compounds and find their principal use as solvents.

10-2 Production from Alcohols. Corresponding primary and secondary alcohols are usually the most suitable sources of aldehydes and ketones, respectively. The essential reaction is the removal of two hydrogen atoms from the alcohol, which may be accomplished either by catalytic dehydrogenation or with the aid of chemical oxidizing agents in solution (wet oxidants).

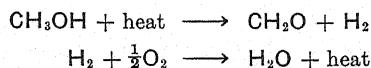
1. *Catalytic dehydrogenation* can be effected by passing the vapors of a primary or secondary alcohol over a suitable catalyst, *e.g.*,



Dehydrogenation is an endothermic reaction, and the alcohol vapors must be preheated to the required temperature. The exit gases are cooled quickly and scrubbed free of acetone; hydrogen may be recovered

for use. Acetaldehyde is manufactured in like manner by the catalytic dehydrogenation of ethyl alcohol.

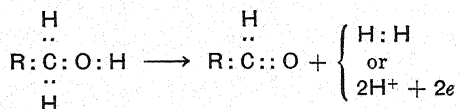
2. *Dehydrogenation and oxidation.* The heat necessary for dehydrogenation can be provided by a simultaneous, exothermic, oxidation reaction. Thus, formaldehyde is usually manufactured by passing the vapors of methanol mixed with a suitable volume of air over a catalyst of copper or silver gauze; once the catalyst is brought to the necessary temperature (450 to 600°C), combustion of part of the free hydrogen maintains it there:



The quantity of hydrogen burned and the temperature attained are controlled by the amount of air admitted and rate of flow over the catalyst (usual contact time about 0.01 second).

3. *Wet Oxidants.* Primary and secondary alcohols can be converted into aldehydes and ketones, respectively, by heating them with water solutions of laboratory oxidizing agents such as dichromic acid or potassium permanganate. Thus, propionaldehyde is prepared in about 50 per cent yield by dropping a water solution of $\text{K}_2\text{Cr}_2\text{O}_7$ and H_2SO_4 into boiling *n*-propyl alcohol; a mechanical stirrer promotes the rapid escape of propionaldehyde (b.p. 48.8°C) but, even so, some is lost through further oxidation to propionic acid (Sec. 10-12). The yields with higher boiling aldehydes are usually unsatisfactory, but the method is useful for the preparation of ketones, which are less subject to further oxidation. A solution of CrO_3 in glacial acetic acid, which also dissolves many water-insoluble organic compounds, is a favored reagent.

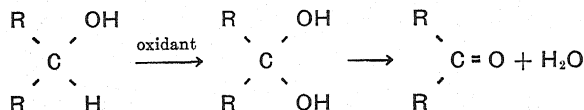
Probably wet oxidation, also, is a process of dehydrogenation. The sensitive point in the alcohol is a hydrogen atom joined to the partially oxidized carbon. This hydrogen atom leaves the organic molecule, together with the hydrogen of the OH group:



Thus the organic molecule *loses electrons* (ordinary definition of oxidation) whether the other product is hydrogen gas or hydrogen ions, formed when the oxidant accepts the electrons.¹

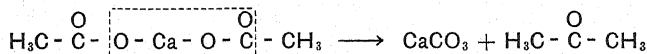
¹The direct loss of electrons occurs at a positive platinum electrode when an acid solution of ethyl alcohol is electrolyzed (though this is complicated by various side

Hydroxylation. The oxidation of certain compounds is interpreted most simply as a process in which an oxygen atom manages to intrude between a carbon and a hydrogen atom. If this were to happen with a secondary alcohol, for example, the initial product would be an *ortho*-ketone (Sec. 10·7); such compounds lose water immediately, *e.g.*,

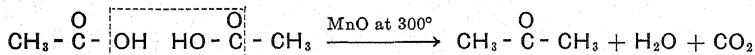


10·3 Other general methods for making aldehydes and ketones include the following:

1. *From Acids.* An important laboratory method for converting carboxylic acids into the corresponding aldehydes is reduction of their acid chlorides (Rosenmund reaction, Sec. 12·10). Another method, which is useful for preparing symmetrical ketones, consists in strongly heating the salt of an organic acid—a process usually known as *dry distillation*. For example, acetone was formerly manufactured by the dry distillation of calcium acetate:



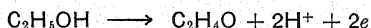
Alternatively, the vapors of an acid may be passed over a suitable oxide catalyst, *e.g.*,



This reaction was formerly used for manufacturing acetone from acetic acid but is now regarded as too expensive.

In a newer procedure, used to some extent, acetone is obtained by passing acetylene and steam through a heated catalyst bed and recovering acetone from the reaction gases. This appears to involve in one operation the hydration of acetylene to

reactions):



We may assume that the same thing happens in oxidation by dichromate, which is reduced as follows:

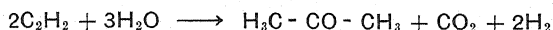


Combining these two partials gives the equation



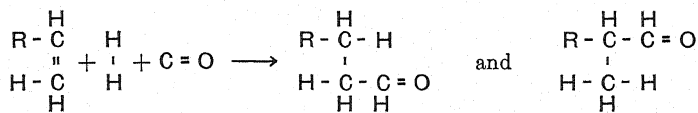
from which one may calculate the amount of the oxidant required.

acetaldehyde, oxidation to acetic acid, and conversion of the latter into acetone. The over-all equation is



2. *From Hydrocarbons.* The controlled oxidation of propane-butane mixtures from natural gas (Sec. 6-19) is becoming an industrial source of formaldehyde, acetaldehyde, acetone, propionaldehyde, etc.

Another method leading to aldehydes is the so-called *Oxo* process, which consists in the catalytic addition of carbon monoxide and hydrogen to an alkene. This is effected at temperatures of 125 to 200°C and pressures of 200 to 300 atmospheres, with the aid of an active cobalt catalyst. The mixture of CO and H₂ adds as though it were formaldehyde, CHO adding to one side of the C=C bond and H to the other:



The aldehydes in the resulting mixture—which is usually more complex than is here indicated—are often reduced to alcohols in a second stage. Any alkene or cyclene may be used, but the method is of special interest as a coming industrial source of higher alcohols and aldehydes not otherwise available.

Aldehydes and ketones are also products of the ozonolysis of alkenes (Sec. 3-13).

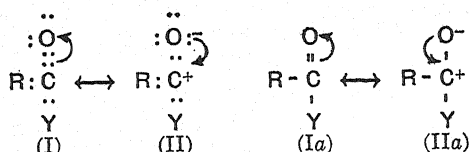
3. The important Friedel-Crafts synthesis of ketones of the types Ar.CO.R and Ar.CO.Ar is described in Sec. 10-18.

4. The acetoacetic-ester synthesis (Sec. 20-17) is useful in preparing certain methyl ketones, H₃C.CO.R, in which R may be branched.

CHEMICAL REACTIONS OF CARBONYL COMPOUNDS

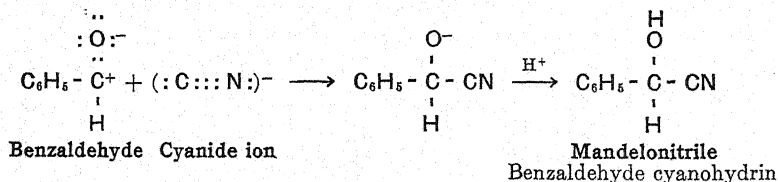
10-4 Addition Reactions. The carbonyl double bond, C=O, like the ethylenic double bond, C=C, represents a condition of unsaturation. This is reflected in the fact that aldehydes and ketones react by addition with many substances. It should be noted, however, that most of the reagents which add to the C=C bond do not add to the C=O bond, and vice versa. Hydrogen, which adds to both these bonds under suitable conditions, is the only important exception.

Aldehydes and ketones have relatively large dipole moments, usually of the order of 2.7 to 3.0 D. From these measured values and the greater electronegativity of oxygen as compared with carbon (Sec. 1-9), it has been calculated that the molecules are resonance hybrids to which the extreme forms (I) and (II) contribute almost equally:

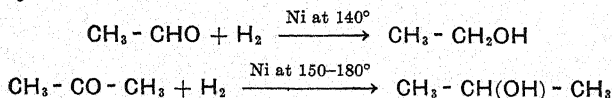


(Y is used to represent either H in an aldehyde or R in a ketone.) The electrical charges on C and O in the actual hybrid are exceptionally large for an organic molecule—amounting to nearly 0.5 unit charge—and may be increased at the moment of reaction through polarization by an approaching reagent (cf. Sec. 3-8). Thus a polar formula (II or IIa) gives the more accurate picture of carbonyl compounds and is more suggestive of the way in which they react.

Such a formula suggests immediately the observed *direction* of carbonyl addition reactions, in which *the more electronegative atom or group from a reagent unites with carbon and the more positive atom or group unites with oxygen*. The polar formula also helps to recall the established mechanism of these reactions, which *begin with the attack of a nucleophilic reagent on the C⁺ atom*. This is illustrated by the *cyanohydrin reaction*¹ in which most aldehydes and many ketones add hydrogen cyanide. The reaction is very slow in pure liquid HCN and is powerfully catalyzed by adding a small amount of any base, which furnishes cyanide ion ($\text{HCN} + \text{B}^- \longrightarrow \text{HB} + \text{CN}^-$). The evidence is strong that reaction begins with the addition of cyanide ion to the carbonyl carbon, after which a proton is added to oxygen, *e.g.*,



10.5 Addition of Hydrogen; Reduction. Aldehydes and ketones add two atoms of hydrogen under appropriate conditions and are thus reduced, respectively, to the corresponding primary and secondary alcohols, *e.g.*

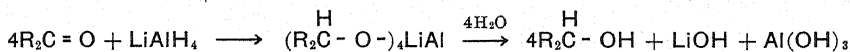


¹ Cyanohydrins are useful intermediates in the preparation of α -hydroxy and α -amino acids. An alternate method of formation is to convert an aldehyde or ketone into its sodium bisulfite addition product (Sec. 10-10) and treat the latter with sodium cyanide.

Finely divided platinum (platinum black) and Raney nickel are effective catalysts for such hydrogenations.

Reduction can be effected also by many chemical combinations capable of producing so-called nascent hydrogen. These include such metals as iron, tin, and zinc with acetic acid or dilute mineral acid, zinc dust with water or sodium hydroxide, or sodium amalgam¹ and water-alcohol. These usually give good yields of primary alcohols from aldehydes; with ketones, *alkaline* reducing agents tend to give pinacols (Sec. 16-9).

Hydride Reductions. Lithium aluminum hydride, LiAlH_4 , is a powerful reducing agent which, since its introduction in 1946, has found many applications in the organic laboratory. It is used in solution in ethyl ether free from water and alcohols, which decompose the reagent with liberation of hydrogen. Aldehydes and ketones are reduced rapidly at room temperature or below and usually with excellent yields. The immediate products are alkoxides, which are hydrolyzed to alcohols by adding water, *e.g.*,



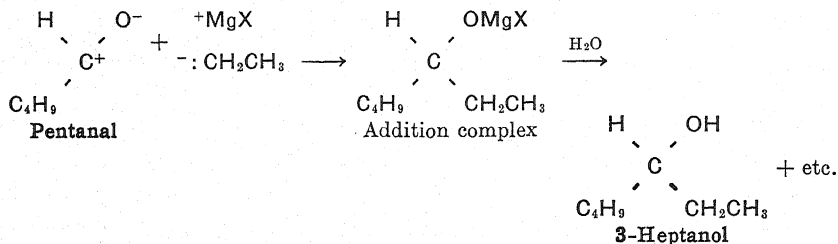
Lithium borohydride, LiBH_4 , a milder reagent, can be used to reduce aldehydes and ketones to alcohols without affecting certain other groups which are reduced by the aluminum compound (Sec. 11-15).

Clemmensen Reduction. When ketones or aromatic aldehydes are heated with amalgamated zinc and concentrated hydrochloric acid, they are reduced to the corresponding *hydrocarbons*. This is important as the most simple and direct method for replacing the carbonyl oxygen by hydrogen. It is useful in preparing pure specimens of hydrocarbons and in simplifying compounds when determining structures.

10-6 Addition of Grignard Reagents. Aldehydes and ketones readily add Grignard reagents. The reaction probably involves the attack by a strongly nucleophilic carbanion furnished by the reagent (Sec. 7-15), upon the $+\delta$ carbon of the carbonyl group. This is followed by the addition of ^+MgX to the negative oxygen atom. When reaction is complete, the addition complex is decomposed by adding water or dilute acid. In this way aldehydes (with the exception of formaldehyde)

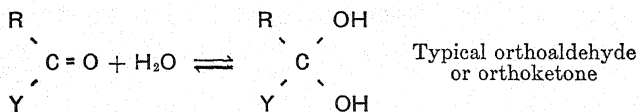
¹ *Amalgams* are alloys of mercury. Sodium amalgam is prepared by adding slowly to warm mercury about 6 per cent of its weight of sodium shavings. The amalgam solidifies on cooling and is then broken into small pieces. When added to a water-alcohol solution of an aldehyde or ketone, hydrogen is evolved slowly but steadily and effects the reduction. Other metals, such as zinc and aluminum, are often *amalgamated* to increase their reactivity. Brief immersion in a solution of mercuric chloride gives a superficial deposit of mercury.

yield higher *secondary* alcohols, *e.g.*,



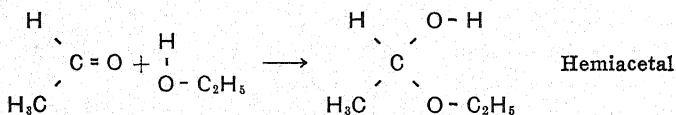
Ketones, reacting in like manner, yield *tertiary* alcohols. These reactions provide a very important laboratory synthesis of many secondary and tertiary alcohols not otherwise obtainable. Formaldehyde is exceptional in yielding a *primary* alcohol; this contains one more carbon atom than the Grignard reagent used.

10.7 Addition of Water and Alcohols. Most compounds which contain two hydroxyl groups attached to the *same* carbon atom are unstable and immediately lose water to form the carbonyl group. Still there is much evidence that aldehydes and ketones, *when dissolved in water*, combine with it to some extent. In other words, it appears that the following reaction is reversible, though ordinarily equilibrium lies far to the left:



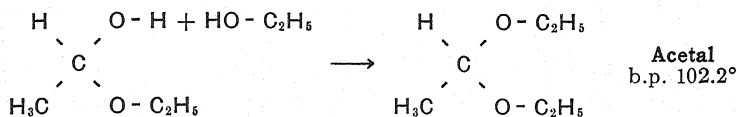
Such hydrated molecules are called, respectively, orthoaldehydes¹ and orthoketones. A very few compounds of this type are stable enough to be isolated (cf. chloral hydrate, Sec. 15.11).

Acetals; Hemiacetals. Acetaldehyde reacts with ethyl alcohol in the presence of acids to give a product called acetal; the initial reaction is the addition of a molecule of alcohol to form a *hemiacetal*.



¹ This terminology comes from inorganic chemistry, where a compound is designated by the prefix *ortho* when the maximum number of hydroxyl groups is attached to a particular atom. Thus, H_4SiO_4 , or $\text{Si}(\text{OH})_4$ is known as orthosilicic acid, and the commoner substance, H_2SiO_3 , derived from it by the loss of a molecule of water, is called metasilicic acid.

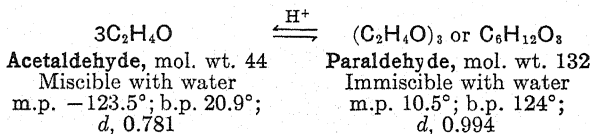
Most hemiacetals react quickly with a second molecule of alcohol, *e.g.*,



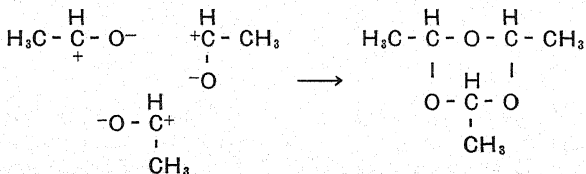
Structurally, acetal is the diethyl ether of orthoacetaldehyde. It resembles other ethers in resisting alkaline hydrolysis, but it is readily hydrolyzed by acids and in this property resembles esters.

Similar compounds, known collectively as *acetals*, are prepared in like manner by reaction between other aldehydes and alcohols in the presence of acid. Ketones do not give good yields of the analogous ketals by this direct method, but such derivatives can be prepared indirectly.

10.8 Polymerization. The lower aldehydes resemble the alkenes in polymerizing readily. Thus, when acetaldehyde is treated with a trace of concentrated sulfuric acid, much heat is evolved and a contraction in volume occurs. These evidences of reaction mark the formation of a cyclic trimer called *paraldehyde*:



Paraldehyde does not give the typical aldehyde reactions, thus indicating the absence of the carbonyl group. On warming with sulfuric acid, it is readily depolymerized and acetaldehyde is regenerated. The ease with which this occurs leads to the conclusion that no new carbon-to-carbon linkage is established when paraldehyde is formed. That reaction is best interpreted as the union of three acetaldehyde molecules by addition at their plus and minus poles, as follows:

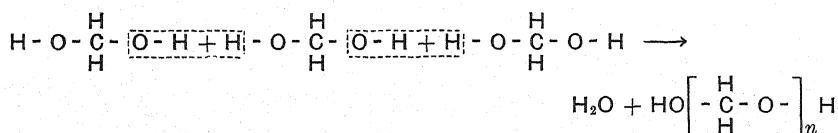


Acetaldehyde also forms a solid polymer (metaldehyde) in which *four* molecules are combined in a ring structure.

Formaldehyde forms a cyclic trimer, $(\text{CH}_2\text{O})_3$, called *trioxane*, with a structure analogous to that of paraldehyde. This is a crystalline solid

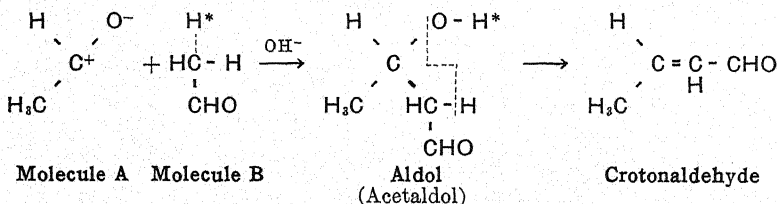
(m.p. 61°C; b.p. 115°C) which is readily soluble in water and many organic liquids. It is stable toward alkalis but is depolymerized by acids.

Under other conditions formaldehyde forms *linear* or *chain* polymers. These arise through the elimination of water between successive molecules of orthoformaldehyde (formaldehyde hydrate) by reactions of the type

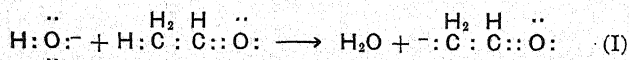


An ordinary water solution of formaldehyde contains much of the simple hydrate and of various polymers in which n is a small number. Evaporation of such a solution leaves a white solid consisting of linear polymers of the same type, in which n has a much higher value. This *paraformaldehyde* is easily depolymerized and is used industrially as a convenient source of formaldehyde solutions and of anhydrous formaldehyde in the manufacture of synthetic resins and various organic syntheses. Trioxane is used similarly.

10.9 Aldol Condensation. Two molecules of acetaldehyde unite in the presence of dilute alkalis to form *aldol*, $\text{C}_4\text{H}_8\text{O}_2$. The latter easily loses water to give crotonaldehyde, $\text{C}_4\text{H}_6\text{O}$, which is usually a product and can be made the major product when desired. The chemical relations of aldol and of crotonaldehyde show that both contain *four-carbon* chains, which proves that the *aldol condensation* (in contrast with polymerization to paraldehyde) involves the formation of a new carbon-to-carbon linkage. The over-all reaction may be pictured as follows:

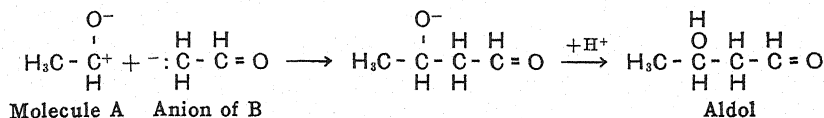


This scheme is an oversimplification because the hydrogen atom H^* does not migrate directly. The function of the base, which is necessary to catalyze the condensation, is to remove a proton from molecule B:

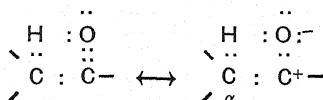


The resulting anion (I) is highly nucleophilic and adds to the carbon of

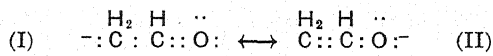
molecule A. The further addition of a proton completes the formation of aldol:



Requirements. Many other condensations of the aldol type are known. Most aldehydes and many ketones can function as A—that is, as the molecule which *accepts* by addition at its C=O bond. To function as B, a compound must contain a *hydrogen atom active enough to be withdrawn as a proton*, from union with carbon, by an alkaline catalyst. This special reactivity is found most frequently in the grouping



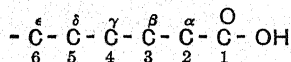
The high electropositive charge on the carbonyl carbon attracts the electrons of the *alpha*¹ carbon; thus an α hydrogen atom is held less firmly and may be withdrawn as a proton by OH⁻ or another base. Removal of the proton is favored also by the resonance which stabilizes the resulting anion. The extreme forms of the hybrid anion from acetaldehyde are



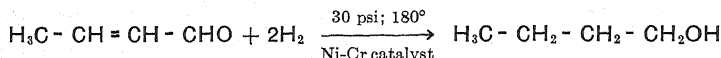
The behavior of higher aldehydes shows that H atoms attached to an α carbon atom are the *only* ones active (acidic) enough to be withdrawn by the alkaline catalysts used. Thus the aldol condensation always occurs at the α carbon of molecule B and an aldehyde such as $(\text{CH}_3)_3\text{C}.\text{CHO}$, having no α hydrogen, cannot function as B.

Applications. The aldol condensation has important industrial uses. Acetaldehyde is condensed to aldol and the latter dehydrated to crotonaldehyde in a single continuous operation, and crotonaldehyde is

¹ In an older system of chemical nomenclature the carbon atom joined directly to the C=O carbon in an aldehyde, a ketone, an acid, or an acid derivative is designated by the Greek letter α , *alpha*. More remote carbon atoms are called, in the order of the Greek alphabet, *beta* (β), *gamma* (γ), *delta* (δ), etc. The somewhat confusing relation between this and the official system, as exemplified by an acid, is

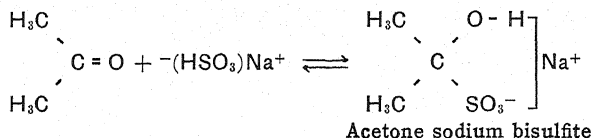


converted to butanol by catalytic hydrogenation:



As much butanol is now produced in this way as by the fermentation process. Thus acetaldehyde has become a significant source of *four*-carbon compounds. The *eight*-carbon alcohol 2-ethylhexanol is produced in a similar way through the aldol condensation of *n*-butyraldehyde.

10-10 Bisulfite Purification. Aldehydes and *methyl* ketones react on shaking with cold, saturated solutions of sodium bisulfite. Considerable heat is evolved and sparingly soluble, crystalline addition products are precipitated. The latter are sodium salts of hydroxy sulfonic acids, formed by reactions of the type



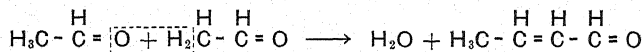
Most ketones fail to react if both groups attached to the carbonyl carbon are larger than methyl.

This reaction is useful in separating an aldehyde or a methyl ketone from impurities, such as an alcohol, which do not react with bisulfite. The latter are removed by filtering off the precipitated addition product and washing it with ether (which is not a solvent for these or other salts). The original aldehyde or ketone can then be liberated by treatment with an acid or a base; either of these removes bisulfite ion



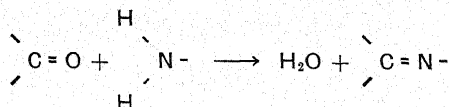
and thus reverses the reaction of formation.

10-11 Removal of the Carbonyl Oxygen. The formation of crotonaldehyde by the aldol condensation is summarized by the over-all equation



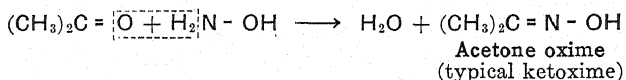
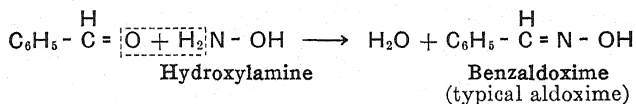
This makes the reaction *appear* to be a simple replacement of the carbonyl oxygen. Similar equations are commonly written to summarize the results of many other condensations and related reactions, such as those outlined below. It is highly probable, however, that each of these proceeds through an addition, followed quickly by the elimination of water or some other simple molecule.

Carbonyl compounds react with various compounds containing the NH_2 group to give products containing a carbon-nitrogen double bond:

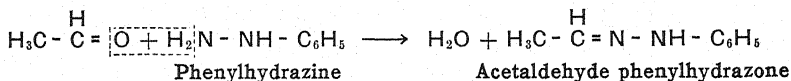


The products are usually crystalline solids of definite melting points and sparingly soluble in water, which are often prepared for the identification of aldehydes and ketones, as follows:

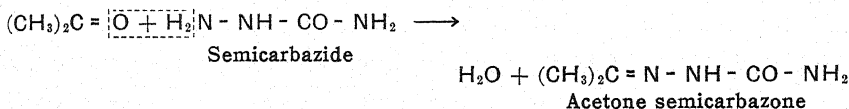
Oximes are formed from aldehydes and ketones by reaction with *hydroxylamine*, *e.g.*,



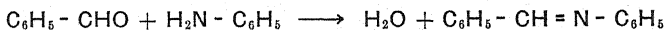
Phenylhydrazones are formed by similar reactions with *phenylhydrazine*. Frequently this reagent is replaced by 2,4-dinitrophenylhydrazine, which gives insoluble products with even the simplest aldehydes and ketones. The reaction is similar with both reagents, *e.g.*,



Semicarbazones are formed by reactions with *semicarbazide*, *e.g.*,

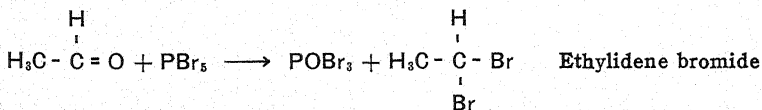


Schiff bases are formed by a similar condensation between aryl aldehydes and amines, *e.g.*,



Reactions with Ammonia. The reactions between aldehydes and the simplest compound containing the amino group, $\text{H}.\text{NH}_2$, are not easily predictable. Acetaldehyde gives a simple addition product, acetaldehyde ammonia, $\text{H}_3\text{C}.\text{CHOH}.\text{NH}_2$; formaldehyde yields hexamethylenetetramine (Sec. 10-13); benzaldehyde forms a complex condensation product called hydrobenzamide.

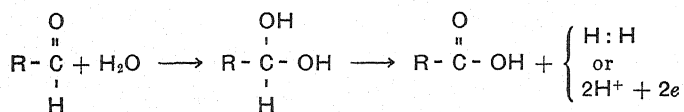
Phosphorus pentahalides replace oxygen by two atoms of halogen, *e.g.*,



This is the only general method for preparing compounds in which two atoms of halogen are attached to the same carbon.

10-12 Oxidation is the reaction in which aldehydes differ most sharply from ketones. Any *aldehyde*, $\text{R}.\text{CHO}$, is readily oxidized to the

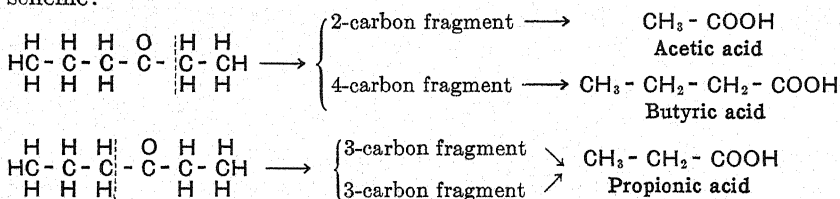
acid containing the same number of carbon atoms, *i.e.*, the corresponding acid. The reaction is regarded as a dehydrogenation of the *ortho*aldehyde:



It occurs easily with aldehydes because they contain a hydrogen atom on the partially oxidized carbon (*cf.* Sec. 10-2, paragraph 3). Very mild oxidizing agents suffice—such as Tollens's reagent and Fehling's solution, which do not affect ketones, alkenes, and most other types of organic compounds. This tendency of aldehydes toward further oxidation explains the low yields ordinarily obtained when they are prepared through the action of wet oxidants on primary alcohols.

Ketones, having no hydrogen atom on the carbonyl carbon, are unaffected by many mild oxidants which act on aldehydes. Vigorous oxidizing agents, such as hot nitric or dichromic acid, split the chain at the carbonyl group, and each fragment is oxidized to an acid. Hence, *on oxidation, a ketone yields at least two acids, neither of which contains as many carbon atoms as the original compound.*

The number of acids possibly formed as oxidation products of a ketone is increased by the fact that the chain may split on either side of the carbonyl carbon (*cf.* Sec. 20-20, paragraph 4). Thus, the ketone 3-hexanone yields a mixture of three different acids, as indicated by the following scheme:



The one-carbon fragment from a methyl ketone is oxidized to formic acid and this, in turn, to carbonic acid (Sec. 11-7); thus carbon dioxide is always one product when a *methyl* ketone is oxidized in the presence of an acid.

INDIVIDUAL ALDEHYDES AND KETONES

10-13 Formaldehyde is a gas (b.p. -21°C) of pungent odor and quite irritant to the membranes of the nose and throat. It is produced¹ mainly from methanol (Sec. 10-2) and to a smaller extent by hydro-

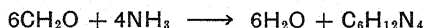
¹ The production of formaldehyde (USA, 1950) was about 835 million pounds (reported as the 37 per cent solution in water).

carbon oxidation (Sec. 6-19). It is sold and used either as *formalin*—a 37 per cent by weight solution in water—or as one of its solid polymers. Some 60 per cent of all the formaldehyde produced is used in the manufacture of plastics (Sec. 23-8). Considerable amounts are consumed in the production of other chemical products such as hexamethylenetetramine and pentaerythritol.

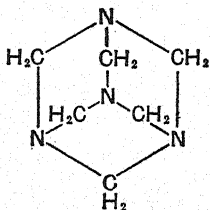
A number of uses for formaldehyde depend upon its action in hardening proteins; these include embalming, preservation of anatomical specimens, manufacture of leather, and hardening of the gelatin emulsions of photographic film. Similar action on living proteins gives formaldehyde a strong germicidal quality which is utilized in disinfecting.

Formaldehyde enters into most of the general reactions of carbonyl compounds described above. In all these it shows exceptionally high reactivity because it is the only aldehyde with two hydrogen atoms on the carbonyl carbon. Formaldehyde also differs from its homologues in the nature of its reactions with certain substances, notably ammonia and alkalies.

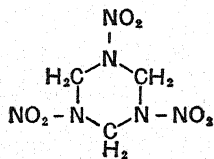
Hexamethylenetetramine. A mixture of formalin and concentrated ammonia evaporated on the water bath leaves a colorless, crystalline solid of the composition $C_6H_{12}N_4$ called *hexamethylenetetramine*, or "hexa":



This compound is a convenient solid source of formaldehyde, which it liberates on contact with acids. It is used for this purpose in the manufacture of plastics and in various laboratory syntheses. It is used also in medicine, under the name methenamine, as a disinfectant for the urinary tract; normal urine is acid enough to effect a slow liberation of formaldehyde.



Hexamethylenetetramine
 $C_6H_{12}N_4 = (CH_2)_6N_4$

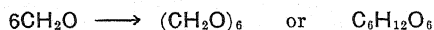


Cyclonite, $C_2H_6N_6O_6$
RDX

Cyclonite; RDX. When hexamethylenetetramine is treated with 98 per cent fuming nitric acid, three of its four six-membered rings are opened and the three nitrogen atoms of the remaining ring are nitrated. The product, cyclonite, or RDX, is one of the most powerful

military high explosives. It was produced on a very large scale during the Second World War for use as the bursting charge in shells and torpedoes and for demolitions. It was often used in admixture with TNT.

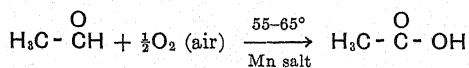
Formaldehyde and Alkalies. On standing at room temperature, a very slightly alkaline solution of formaldehyde is slowly converted into a mixture of sugars containing *carbon chains* of five and six members. This mixture is called *formose*. The reaction is a type of polymerization, the details of which are not clear, which can be summarized by equations of the type



Aldol Condensation; Pentaerythritol. Formaldehyde has no α carbon atom and therefore cannot serve as molecule B (Sec. 10-9) in aldol-type condensations. It does, however, react readily as molecule A in condensations with other aldehydes, *e.g.*, formaldehyde and acetaldehyde condense in the presence of limewater to give pentaerythritol (Sec. 16-15). Initially, three molecules of formaldehyde, acting as A, combine with one of acetaldehyde, acting as B, to form $(\text{CH}_2\text{OH})_3\text{C}\cdot\text{CHO}$. This undergoes a Cannizzaro-type reaction (Sec. 10-17) with a fourth molecule of CH_2O , in which the latter is oxidized to formate ion and the five-carbon aldehyde is reduced to $\text{C}(\text{CH}_2\text{OH})_4$.

10-14 Acetaldehyde. The principal sources of acetaldehyde are the dehydrogenation of ethyl alcohol and the hydration of acetylene (Sec. 3-17). It is also a product of the oxidation of butane (Sec. 6-19) and a by-product in one method for manufacturing acetic anhydride (Sec. 12-12). Acetaldehyde is a very volatile liquid (b.p. 20.9°C) of marked and somewhat sweetish odor, which is freely miscible with water.

Most of the acetaldehyde produced¹ is used on the premises where it is made, for conversion into other chemical compounds. The largest use is for oxidation to acetic acid and acetic anhydride, *e.g.*,



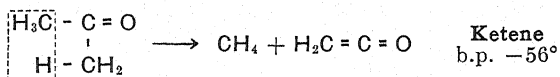
Acetic anhydride is obtained under similar conditions, in the presence of an excess of acetic acid. Another large use is in the manufacture of butanol through crotonaldehyde (Sec. 10-9).

Aldehyde Resin. The aldol condensation is effected by the use of very dilute alkali. With more concentrated alkali solutions, particularly on warming, a solution of acetaldehyde turns yellow or brown and acquires a caramellike odor; there are formed complex resinous condensation products of unknown structure and molecular weight, which as yet lack practical application. Other lower aliphatic aldehydes, except formaldehyde, behave in like manner.

¹ Annual production of acetaldehyde in the United States is of the order of 500 million pounds.

10-15 Acetone is manufactured¹ principally by the catalytic dehydrogenation of isopropyl alcohol, and some is obtained as a co-product in the fermentation process for butanol (Sec. 8-21). Its major uses depend upon its solvent powers. More than half of the production is used to dissolve cellulose acetate in the manufacture of rayon; large quantities are used as a solvent for acetylene and in the production of lacquers, etc. Major chemical uses are the production of ketene and methyl methacrylate (Sec. 15-19).

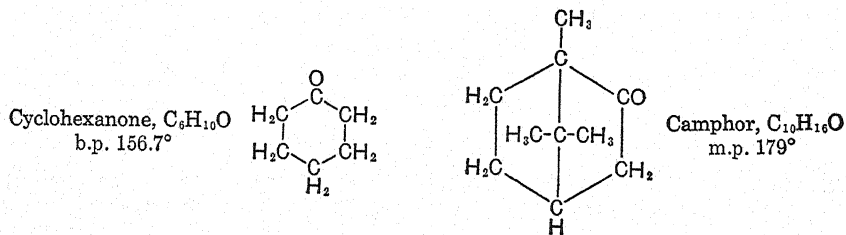
Ketene is an unsaturated ketone of unusual structure. It is manufactured by passing acetone vapors rapidly through a chrome-iron tube at 650 to 670°C:



It is made also, in similar fashion, from acetic acid. Ketene is a poisonous and highly reactive gas. It forms addition products with many types of compounds which contain either the OH or the NH₂ group. The major present use is the production of acetic anhydride (Sec. 12-12) by addition of acetic acid.

10-16 Alicyclic Ketones. The two compounds of outstanding industrial importance in this class are cyclohexanone and camphor.

Cyclohexanone is manufactured in large quantities by the catalytic dehydrogenation of cyclohexanol and by the regulated oxidation of cyclohexane. It is used as an industrial solvent and, in much larger amounts, for further oxidation to adipic acid in the manufacture of nylon (Sec. 19-7).

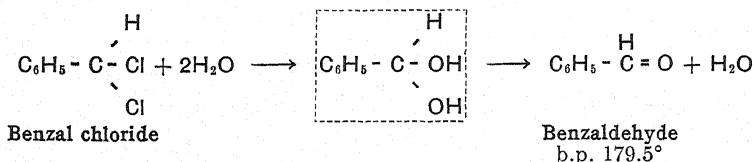


Camphor is a bicyclic ketone related to the terpenes. It is a solid of familiar odor, occurring naturally in the camphor tree, which is cultivated extensively in Japan and Formosa. Large amounts are now manufactured synthetically from pinene. Its major use is as a plasticizer.

Some large-ring alicyclic ketones are mentioned in Section 19-8.

¹ The production of acetone (USA, 1950) amounted to nearly 500 million pounds; only about 5 per cent comes from the fermentation process.

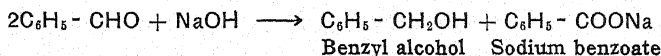
10-17 Aromatic Aldehydes. Benzaldehyde, $\text{C}_6\text{H}_5\text{CHO}$, is the most important aromatic aldehyde. It is readily formed by the oxidation of benzyl alcohol but is always manufactured from toluene. The commonest method involves side-chain halogenation to benzal chloride, which is then hydrolyzed by boiling water in the presence of a small amount of acid or alkali:



Benzaldehyde is manufactured also by the regulated oxidation of toluene in the vapor phase (with air, over a catalyst at 500°C) and, in the liquid phase, by the action of sulfuric acid and manganese dioxide.

Benzaldehyde is a colorless liquid practically insoluble in water and with a characteristic pleasant odor. It is used to some extent as a food flavor under the name *synthetic oil of bitter almonds*.¹ Benzaldehyde enters into most of the typical reactions of the aliphatic aldehydes, though rather less readily. Major differences are the following.

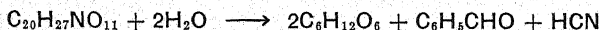
Cannizzaro Reaction. When benzaldehyde stands with a cold concentrated solution of sodium or potassium hydroxide, half of its molecules are reduced to benzyl alcohol and half are oxidized to benzoic acid:



This type of reaction, in which one molecule of a compound is oxidized at the expense of another, is called a *dismutation*. The Cannizzaro reaction is limited to those aldehydes which do not contain an *alpha* hydrogen atom.

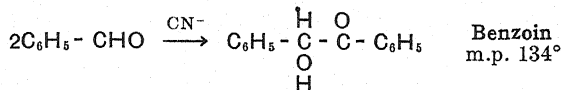
Condensations. Benzaldehyde can function as molecule A in the aldol-type condensations (Sec. 10-9) and does so with various compounds, *e.g.*, acetaldehyde and acetone. The products may have the aldol structure, or they may be unsaturated like crotonaldehyde. Closely

¹ Bitter almond, peach, and apricot kernels contain a glucoside called *amygdalin*, $\text{C}_{20}\text{H}_{27}\text{NO}_{11}$. When such seeds are macerated with cold water, amygdalin is hydrolyzed by the enzyme *emulsin*, also present, into glucose, benzaldehyde, and hydrocyanic acid:



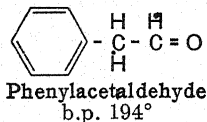
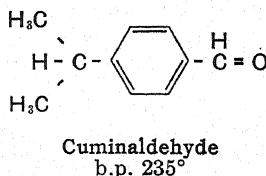
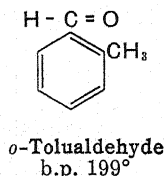
The distillate, consisting of benzaldehyde and hydrocyanic acid, is known as the *volatile oil of bitter almonds*. The hydrocyanic acid is readily removed by fractional distillation or by chemical reagents. This was the original source of benzaldehyde as studied by Liebig and Wöhler in 1837.

related are its condensations with acetic anhydride to form cinnamic acid (Perkins synthesis, Sec. 15-22) and its reactions with phenols and with aryl amines to form dyes. Under the influence of cyanide ion, which is a specific catalyst for this reaction, two molecules of benzaldehyde unite to form benzoin:



Autoxidation. Benzaldehyde is highly susceptible to oxidation by atmospheric oxygen in the presence of light and of certain catalysts, such as traces of iron compounds; when a few drops are allowed to stand on a watch glass, crystals of benzoic acid soon appear. Under some conditions good yields of perbenzoic acid, $\text{C}_6\text{H}_5\text{-CO.OOH}$, are obtained. These products of autoxidation result from a chain reaction, or reactions, in which a peroxide and a benzoyl free radical are probable intermediates. Various substances which are normally stable toward atmospheric oxygen are readily oxidized in the presence of benzaldehyde or other substance undergoing autoxidation. Small amounts of an inhibitor—*i.e.*, a reducing substance such as hydroquinone—prevent autoxidation by reacting with an intermediate and thus breaking the chain.

Other aromatic aldehydes include

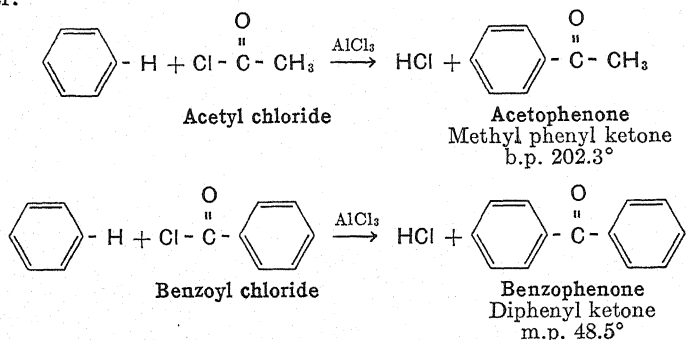


Those which have the CHO group attached directly to the aryl nucleus resemble benzaldehyde in their chemical properties. Phenylacetaldehyde is more nearly like an aliphatic compound of about the same molecular weight; it is used as a perfume (hyacinth), as are various other higher aldehydes and ketones.

10-18 Aryl Ketones; Friedel-Crafts Synthesis. Aromatic hydrocarbons¹ yield ketones by reaction with acid chlorides (Sec. 12-9) in the

¹ This reaction is typical of aromatic compounds in general, except those which contain a strongly deactivating group (Sec. 5-20) attached to the nucleus. Acid anhydrides (Sec. 12-11) may be used instead of acid chlorides. It is necessary to use somewhat more than one mole of AlCl_3 per mole of the other reactants because aluminum chloride adds to carbonyl compounds, forming oxonium complexes. When the reaction is ended, water or dilute acid is added to decompose the complex and liberate the ketone.

presence of anhydrous AlCl_3 . The following over-all reactions are typical:



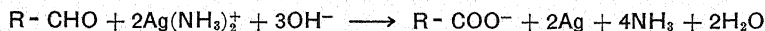
This application of the Friedel-Crafts reaction (cf. Sec. 22-5) is the most useful general method for preparing ketones in which at least one aryl nucleus is joined to the carbonyl carbon atom. The yields are much better than in alkylations (Sec. 5-14); the carbonyl group is deactivating, and reaction stops short when one nuclear hydrogen atom has been replaced; and, unlike alkyl halides, acid chlorides are not rearranged by contact with aluminum chloride.

Aryl ketones enter rather sluggishly into the typical carbonyl addition reactions; otherwise, their chemical properties require no special comment.

10-19 Recognition. Aldehydes and ketones can be distinguished from other types of neutral compounds by the fact that all give colored, insoluble precipitates with 2,4-dinitrophenylhydrazine (Sec. 10-11). Aldehydes are distinguished from ketones by their positive reactions in the Schiff and Tollens tests. Most aldehydes also reduce Fehling's solution (Sec. 20-9); benzaldehyde and ketones do not.

Schiff's Test. Schiff's reagent is a water solution of the red dyestuff pararosaniline which has been decolorized, or changed to a pale straw-yellow, by passing in sulfur dioxide. An aldehyde combines with the sulfurous acid and converts the dye into a colored compound. A marked coloration—pink, red, purple—appearing *at once*, indicates an aldehyde; pure ketones give no immediate color. The reagent is used at room temperature.

Tollens's reagent is prepared by adding a little sodium hydroxide to a solution of silver nitrate, followed by just enough dilute ammonia to dissolve the precipitate of silver oxide-hydroxide. Most of the silver is in the form of the complex silver-ammonia ion, which is reduced by aldehydes at room temperature to metallic silver:



The silver may appear either as a finely divided black precipitate or, if the walls of the test tube are quite clean, as a shining mirror. Tollens's reagent is a very mild oxidizing agent.

Derivatives for the final identification both of aldehydes and ketones are usually phenylhydrazones, 2,4-dinitrophenylhydrazones, oximes, or semicarbazones prepared by the reactions given in Section 10-11. Oxidation to the corresponding solid acid is

often satisfactory for aromatic aldehydes. *Methyl* ketones can be oxidized to acids ($\text{R.CO.CH}_3 \longrightarrow \text{R.COOH}$) by the haloform reaction (Sec. 15-10).

Questions

1. (a) Describe the essential similarity and difference in the structure of aldehydes and ketones. (b) Why is acetone the simplest possible ketone? (c) Show why corresponding aldehydes and ketones derived from alkanes are necessarily isomers.

2. Explain the lower boiling points of aldehydes and ketones in comparison with those of the alcohols from which they are derived.

3. Give the common names and the systematic names of: (a) the C_5 normal primary alcohol, aldehyde, and acid (Table 11-1); (b) all the possible five-carbon saturated ketones.

4. Discuss and illustrate by specific examples three general methods for making aldehydes and ketones from corresponding alcohols.

5. Why is it important to cool the reaction products quickly when an aldehyde or ketone is prepared by catalytic dehydrogenation of an alcohol?

6. Methyl ethyl ketone and methyl isobutyl ketone are gaining in importance as industrial solvents with boiling points higher than acetone. Both are made from the corresponding alcohols which, in turn, are produced by the hydration of alkenes (Sec. 8-20). Select the necessary alkenes and write equations for the series of reactions involved.

7. Write the structural formulas of the products to be expected from 1-pentene in the Oxo process.

8. (a) Summarize the direction of addition to carbonyl groups and explain its origin. (b) Explain and illustrate with a specific example the mechanism of addition to carbonyl groups.

9. Show by means of structural equations how the following alcohols can be obtained from the given aldehyde or ketone (with the aid of any Grignard reagent which may be needed): (a) 3-hexanol from *n*-butyraldehyde; (b) diethyl phenyl carbinol from 3-pentanone; (c) diphenyl carbinol from benzaldehyde; (d) triphenyl carbinol from benzophenone; (e) diphenyl carbinol from benzophenone.

10. Explain accurately why formaldehyde is the only aldehyde which can yield *primary* alcohols through the addition of Grignard reagents.

11. Write structural equations for the formation of cyclic and chain polymers of formaldehyde.

12. (a) Discuss the mechanism of the aldol condensation, illustrating with propionaldehyde. (b) Show how the immediate product would react on heating. (c) Diacetone alcohol, $\text{CH}_3\text{CO.CH}_2\text{C(OH)(CH}_3)_2$, b.p. 168°C , is a useful solvent made by the condensation of acetone. Write structural equations for the over-all reaction of formation and for the further change by which it yields mesityl oxide (a compound related to it as is crotonaldehyde to aldol). (d) Write the formulas of two aliphatic aldehydes which cannot function as molecule B in an aldol-type condensation.

13. Methanol and acetone form a constant boiling mixture. Outline a method for obtaining *pure* methanol from a specimen containing 2 per cent of acetone.

14. Why is very *brief* contact with the catalyst important in producing an aldehyde by dehydrogenation-oxidation of a primary alcohol?

15. Acetaldehyde is a major source of acetic acid, and other acids are readily obtained by oxidation of the corresponding aldehydes, when available. Explain: (a) why the oxidation of ketones is not, in general, a satisfactory preparative method for acids; (b) why the oxidation of cyclohexanone is an exception to this rule and show the expected product.

16. Write the full series of reactions involved in the production of: (a) acetone from propene; (b) butanol from acetylene; (c) 2-ethylhexanol from butyraldehyde.

17. Show the structural formula of an aliphatic aldehyde other than CH_2O which would be expected to enter into the Cannizzaro reaction and write the equation for the reaction.

18. Explain why benzaldehyde should be stored in filled, well-stoppered, brown-glass bottles or cans.

19. (a) Explain why good yields of benzophenone can be obtained by the oxidation of diphenylmethane while no acetophenone results from the oxidation of ethyl benzene. (b) What is the actual product of the latter reaction? (c) Why is benzophenone less readily oxidized than most other ketones?

20. Outline a method, not based on fractional distillation, by means of which pure phenol, benzyl alcohol, and benzaldehyde can be obtained from a mixture consisting of equal parts of the three substances. (Assume that all three are insoluble in water.)

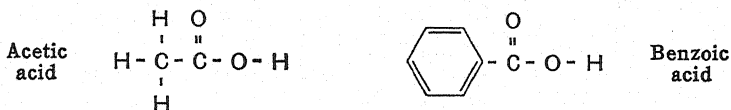
21. Write structural equations for the principal reaction or reactions to be expected under the following conditions: (a) Isopropyl alcohol is refluxed with a solution of sodium dichromate and sulfuric acid. (b) Ethyl alcohol vapors, mixed with a limited supply of air, are passed over a silver gauze, initially heated to reaction temperature. (c) The dry calcium salt of butyric acid ($\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$) is strongly heated. (d) The vapors of propionic acid, $\text{CH}_3\text{CH}_2\text{COOH}$, are passed over a heated manganese oxide catalyst. (e) Toluene and propionyl chloride, $\text{CH}_3\text{CH}_2\text{COCl}$, are treated with anhydrous AlCl_3 .

22. Write structural equations for the reactions, if any, to be expected under the following conditions: (a) An alcoholic solution of benzaldehyde is treated with sodium amalgam. (b) Butyraldehyde is refluxed with a solution of dichromic acid. (c) Acetone is treated with a solution of hydrogen cyanide containing some sodium cyanide. (d) Methyl ethyl ketone is shaken with a cold, saturated solution of sodium bisulfite. (e) The product of (d) is warmed with a solution of sodium carbonate. (f) 4-Methyl-3-heptanone is refluxed with a vigorous oxidizing agent. (g) Acetaldehyde is treated with Tollens's reagent. (h) *o*-Tolualdehyde is shaken with a cold, concentrated solution of potassium hydroxide. (i) Butyraldehyde and ethyl alcohol are mixed and treated with a dilute acid. (j) Cyclohexanone is treated with a solution of 2,4-dinitrophenylhydrazine. (k) Acetophenone is treated with hydroxylamine. (l) Benzophenone is treated with zinc and concentrated hydrochloric acid.

CHAPTER 11

CARBOXYLIC ACIDS

Compounds which contain the carboxyl group, COOH , have acidic properties and are called carboxylic acids, *e.g.*,



The word *carboxyl* is a contraction of *carbonyl* and *hydroxyl* and suggests the structure in which the $\text{C}=\text{O}$ and OH groups are combined as shown above.

The present chapter considers only the monocarboxylic acids, *i.e.*, those which contain *one* COOH group. All these can be represented by the type formula $\text{R}.\text{COOH}$, in which R stands for a hydrocarbon radical which may be aliphatic, alicyclic, or aromatic.

11.1 Homologous Series of Fatty Acids. We may regard acetic acid as a compound derived from ethane by the oxidation of a CH_3 group to COOH . The many acids which bear a like relationship to the other alkanes form a homologous series of the general formula $\text{C}_n\text{H}_{2n}\text{O}_2$. Some of the higher members, such as palmitic and oleic acids, were first obtained from the fats, which they resemble in physical properties. Thus arose the term *fatty acid*, which is now commonly applied to all members of this series—although the lower ones neither occur in the fats nor in any way resemble them. The common names, formulas, and physical constants of some of these acids are given in Table 11.1.

Nomenclature. The systematic names of the fatty acids are formed from those of the parent hydrocarbons by replacing the terminal *-e* by *-oic* and adding the word *acid*, *e.g.*, $\text{CH}_3.\text{CH}_2.\text{CH}_2.\text{COOH}$, *butanoic acid*. Such names are seldom used for the commoner acids. Because of their wide occurrence in nature, many of these were isolated long ago and given names suggested by some physical property or natural source; thus, stearic acid was so called because it is a solid (Gr., *stereos*), and butyric acid gets its name from its occurrence in butter. These names (Table 11.1) are still in common use.

11.2 Structure and Physical Properties. Still thinking of the fatty acids as compounds derived from the alkanes by oxidizing a CH_3 group

TABLE 11-1 HOMOLOGOUS SERIES OF NORMAL FATTY ACIDS

Acid	Formula	Melting point, °C	Boiling point, °C	Density	$K \times 10^5$
Formic.....	H.COOH	8.6	100.8	1.220	17.72
Acetic.....	CH ₃ .COOH	16.7	118.1	1.049	1.76
Propionic.....	CH ₃ .CH ₂ .COOH	-22	141.1	0.992	1.34
Butyric.....	CH ₃ .(CH ₂) ₂ .COOH	-4.7	163.5	0.964	1.50
Valeric.....	CH ₃ .(CH ₂) ₃ .COOH	-34.5	187	0.939	1.38
Caproic.....	CH ₃ .(CH ₂) ₄ .COOH	-3.2	202	0.875 ^{84°}	1.32
Caprylic.....	CH ₃ .(CH ₂) ₆ .COOH	16.3	239.7	Gradual decrease ↓ 0.839 ^{84°}	Little further change ↓
Pelargonic.....	CH ₃ .(CH ₂) ₇ .COOH	12.3	255.6		
Capric.....	CH ₃ .(CH ₂) ₈ .COOH	31.2	270		
Lauric.....	CH ₃ .(CH ₂) ₁₀ .COOH	43.9	299		
Myristic.....	CH ₃ .(CH ₂) ₁₂ .COOH	54.1			
Palmitic.....	CH ₃ .(CH ₂) ₁₄ .COOH	62.7			
Margaric.....	CH ₃ .(CH ₂) ₁₅ .COOH	60.9			
Stearic.....	CH ₃ .(CH ₂) ₁₆ .COOH	69.6	376†	0.839 ^{84°}	
Arachidic.....	CH ₃ .(CH ₂) ₁₈ .COOH	74.2			
Behenic.....	CH ₃ .(CH ₂) ₂₀ .COOH	79.7			
Melissic.....	CH ₃ .(CH ₂) ₂₈ .COOH	93.6			

† Value obtained by extrapolation of vapor pressures at lower temperatures.

to COOH, we may look for the physical effects of this change by comparing the properties of ethane and acetic acid. Such a comparison is made in Table 11-2.

TABLE 11-2 PROPERTIES OF ETHANE AND ACETIC ACID

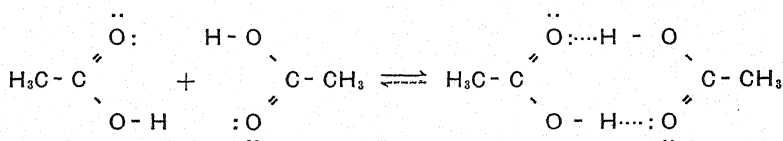
Property	Ethane, H ₃ C.CH ₃	Acetic acid, H ₃ C.COOH
Molecular weight.....	30	60
Melting point.....	-183.2°	16.7°
Boiling point.....	-88.6°	118.1°
Density.....	0.546 (at b.p.)	1.049
Solubility in water.....	Trace only	Freely miscible
Conductivity of water solutions.....	Nonconductor	Fair conductor

Summarizing, it appears that the conversion of CH₃ into COOH raises both melting point and boiling point by some 200°C; approximately doubles the density; converts a water-insoluble compound into one that is freely soluble; and changes a nonelectrolyte into a compound which is a fair conductor in solution. Similar effects always accompany the introduction of the carboxyl group but, as in other series, they become less marked in the higher members. Hence, with increasing length of the

alkyl radicals, physical properties shift progressively toward those of the parent hydrocarbons.

The fatty acids through C_4 are miscible with water in all proportions, but above this water solubility rapidly decreases until, at C_8 and higher, the acids are practically as insoluble as their parent hydrocarbons. All are readily soluble in organic solvents such as ether, chloroform, and benzene. The acids from butyric to capric, C_{10} , possess strong, disagreeable odors. Density decreases with the lengthening carbon chain, and all except formic and acetic acids are lighter than water. Through capric acid (b.p. 270°C) they can be distilled unchanged at atmospheric pressure, though distillation with steam is usually preferable; with more than 10 carbon atoms they decompose instead of distilling, except at greatly reduced pressures. Broadly speaking, melting points rise with increasing chain length, but the melting point of an acid with an *odd* number of carbon atoms is usually below that of the next lower acid with an even number. This is a result of a difference in the ease with which they pack into a crystal lattice.

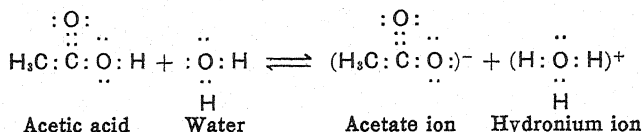
11.3 Association of Acids. The abnormally high boiling point of acetic acid suggests that its molecules are associated. Further, its observed molecular weight in a nonionizing solvent such as benzene is approximately 120, or about twice the value of 60 calculated for single molecules. The vapor of acetic acid shows the same abnormality. This is part of the evidence which leads to the conclusion that the acid exists mainly as a *cyclic dimer*, held together by rather strong hydrogen bonds, as follows:



Similar evidence for this type of association has been obtained with formic, benzoic, and other acids.

Hydrogen bonding with *water* molecules helps to explain the effect of the carboxyl group in increasing water solubility. This effect is evident even in the higher acids such as stearic, $C_{17}H_{35}\text{COOH}$, where the COOH group is unable to pull the long hydrocarbon "tail" into solution. Langmuir dissolved stearic acid in acetone and poured the dilute solution on water, where the acetone either evaporated or was dissolved. By suitable measurements he was able to show that the stearic acid molecules arranged themselves perpendicularly to the surface of the water, with their COOH ends drawn down into it and the hydrocarbon radicals pointing upward.

11.4 Ionization. The carboxylic acids differ from their parent hydrocarbons, from the alcohols, and from most other classes of carbon compounds¹ in that they release protons when dissolved in ionizing solvents such as water, *e.g.*,



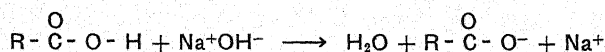
They are, however, weak acids as may be seen from Table 11-3. These figures show that formic and benzoic acids are somewhat stronger than acetic, and that the higher fatty acids are slightly weaker, but that all are of the same general order of strength. This is well below that of the common inorganic acids but well above carbonic acid and far above phenol.

TABLE 11-3 RELATIVE STRENGTH OF SOME ACIDS

Acid	In tenth molar solution		Ionization constant, K_a
	Percentage ionization	Relative numbers of molecules ionized	
Hydrochloric acid, HCl.....	100.	1 in 1	†
Formic acid, H.COOH.....	4.63	1 in 20	1.77×10^{-4}
Benzoic acid, C ₆ H ₅ .COOH.....	2.57	1 in 40	6.6×10^{-5}
Acetic acid, CH ₃ .COOH.....	1.34	1 in 75	1.76×10^{-5}
Higher fatty acids, R.COOH....	1.24	1 in 80	<i>ca.</i> 1.4×10^{-5}
Carbonic acid, HO.COOH.....	0.17	1 in 600	3×10^{-7}
Phenol, C ₆ H ₅ .OH.....	0.004	1 in 25,000	1.3×10^{-10}

† The ionization constant of hydrochloric acid is too large to be measured in aqueous solution.

The ionization of carboxylic acids, even though quite limited in pure water, enables bases to convert them completely, through neutralization, into the ions of their salts:



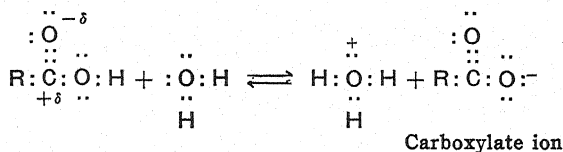
Nearly all sodium and potassium salts are freely soluble in water. Hence, *water-insoluble carboxylic acids dissolve in dilute solutions of sodium and potassium hydroxides* (the general classification test for acidic organic

¹ Phenols, sulfonic acids, and enols (Sec. 20-14) have more or less pronounced acidic properties.

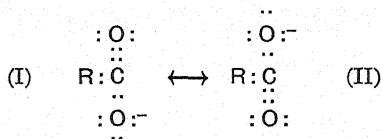
compounds, Sec. 8 27). Because they are stronger acids than carbonic, they also dissolve in solutions of Na_2CO_3 and of NaHCO_3 , in which respect they differ from unsubstituted phenols.

11.5 Why Carboxylic Acids Ionize. Why does the OH hydrogen atom ionize in acetic acid but not in ethyl alcohol? The answer must be sought in some effect of the $\text{C}=\text{O}$ oxygen atom which is present in the acid. This effect is due in part to induction by the electronegative oxygen atom and, in part, to the resonance which its presence makes possible.

Electron attraction by the $\text{C}=\text{O}$ oxygen atom places a relatively high $+\delta$ charge on the $\text{C}=\text{O}$ carbon, as was noted in connection with the aldehydes and ketones (Sec. 10.4). This $+\delta$ charge operates in the acid to attract electrons of the OH oxygen; hence, the OH hydrogen is less tightly bound than in an alcohol and more readily drops off with a water molecule:

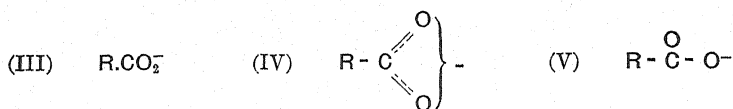


Probably a more important factor is resonance in the carboxylate ion between equivalent extreme forms which may be represented as

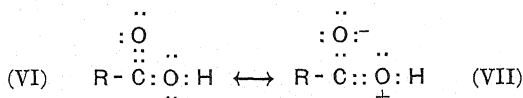


This stabilization of the ion by the energy of resonance increases its tendency to be formed and decreases its tendency to pick up a proton from the solution and thus reverse the ionization reaction.

Physical evidence for resonance in the carboxylate ion is furnished by X-ray diffraction measurements on acetates and other salts. These show the same bond length between carbon and *both* oxygen atoms—a value intermediate between those for double and single carbon-oxygen bonds. The unit negative charge is also shared equally by the two oxygen atoms. As with other resonance hybrids, there is no satisfactory way to show this by a single formula. We may evade the issue as in (III), or adopt some conventional symbol as in (IV), or assign the charge arbitrarily to one of the oxygen atoms as in (V)—which is ordinarily used.



Resonance in the acid molecule is also possible and exists, but to a lower degree than in the carboxylate ion. The contributing forms are the ordinary one (VI) and another (VII) which we can imagine as being formed from it by the electron shift indicated:



These two forms are *not* identical, and (VII) is improbable because its formation involves the setting up of opposite (+ and -) charges within the molecule. Such a *separation of charges* tends strongly to be reversed. Hence, we must regard the actual state of the acid molecule as much closer to (VI) than to (VII). An effect of resonance may be seen, however, in the reluctance of carboxylic acids to enter into the addition reactions to be expected of compounds containing a true C=O group.

11-6 Acetic acid is the most important of all organic acids. It can be made in the laboratory by oxidizing either ethyl alcohol or acetaldehyde and is manufactured in very large quantities¹ by the catalytic oxidation of the latter with air (Sec. 10-14). This process yields the substantially anhydrous acid (99 per cent or better). Acetic acid is also produced to some extent in the wood-distillation industry and by a fermentation process which yields only dilute solutions (manufacture of vinegar).

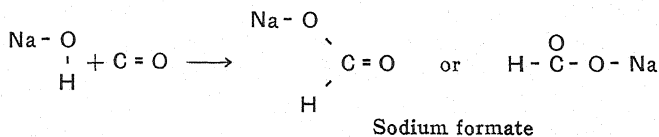
When chilled, the pure compound solidifies to a crystalline mass resembling ice; for this reason the anhydrous acid is known as *glacial* acetic acid. The crystals melt at 16.7°C to a liquid of sharp odor which distills without decomposition at 118.1°C. Anhydrous acetic acid is freely miscible with hydrocarbons and most other types of organic liquids; it is also miscible with water in all proportions.

Uses. Concentrated acetic acid is used in large quantities in the manufacture of cellulose acetate, vinyl acetate, many solvent esters such as ethyl acetate and butyl acetate, and inorganic salts, *e.g.*, sodium, lead, copper, and other acetates. The dilute acid is used extensively in textile finishing, dyeing, tanning, and many other industrial operations requiring a low but fairly constant acidity. In the form of vinegar, dilute acetic acid is widely used as a food preservative and condiment.

11-7 Formic acid, H.COOH, gets its name from the fact that it was first obtained from the bodies of ants (*L., formica*). It can be made by

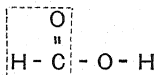
¹ The production of synthetic acetic acid (USA, 1950) amounted to 440 million pounds. In addition, nearly five times this amount was "recovered" from acetylation processes such as the manufacture of cellulose acetate.

the regulated oxidation of methanol or formaldehyde, but is manufactured by heating sodium hydroxide with carbon monoxide at a pressure of 6 to 10 atmospheres:

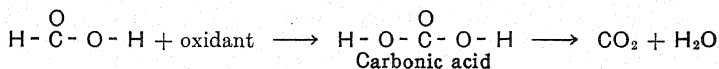


Formic acid is liberated by treating sodium formate with somewhat dilute sulfuric acid; it is distilled off at reduced pressure and is concentrated by fractionation. It is a colorless caustic liquid of pungent odor, freely miscible with water, alcohol, and ether. Formic acid is used for making its salts and esters (formates), for the coagulation of rubber latex, and for other technical operations. Sodium formate is used in large quantities for the manufacture of oxalic acid.

Formic is the only acid in which a *hydrogen atom* is attached to the carbon of a carboxyl group. It therefore contains the typical aldehyde grouping,



As a result of this unique structure, it differs from its homologues in a number of properties. Especially noteworthy is the ease with which formic acid and the formates are oxidized—whence their effectiveness as reducing agents. While the other fatty acids are unaffected by permanganates and dichromic acid, formic acid and the formates are oxidized by such mild reagents as mercuric and silver salts. The reaction involves the oxidation of the hydrogen atom to hydroxyl, *i.e.*, the conversion of formic into carbonic acid:



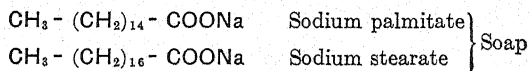
This explains why no formic acid is obtained in reactions where methanol or formaldehyde is formed in the presence of a strong oxidizing agent, *e.g.*, in the oxidation of methyl ketones. Formic acid also differs from its homologues in yielding no acid chloride and no anhydride. When heated with sulfuric acid or other dehydrating agent, *carbon monoxide* is evolved.

Strength of Formic Acid. It is apparent from Table 11 1 that formic acid is considerably more highly ionized than any of the other fatty acids. This is a further consequence of the fact that formic acid is the only

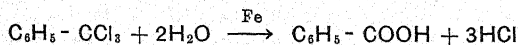
one in which a hydrogen atom is attached to the carboxyl carbon. Because the hydrogen atom is less electron-releasing than a methyl group the carboxyl carbon in H.COOH has a higher $+\delta$ charge than in $\text{H}_3\text{C.COOH}$. Consequently this carbon atom has more attraction for the oxygen electrons and the COOH proton is released more readily. The same argument explains why the acid $(\text{H}_3\text{C})_3\text{C.COOH}$ is weaker than acetic and weaker also than its isomer $\text{H}_3\text{C.CH}_2\text{CH}_2\text{COOH}$.

11-8 Higher Fatty Acids. The more important of the higher fatty acids are those which occur, as their glycerol esters, in the natural fats and fatty oils (Sec. 16-16). These are usually compounds of *normal* chain structure, containing an *even* number of carbon atoms. All are quite similar in chemical properties since these depend upon reactions of the carboxyl group present in all of them.

Palmitic acid, $\text{C}_{16}\text{H}_{32}\text{O}_2$ (m.p. 62.7°C), and *stearic* acid, $\text{C}_{18}\text{H}_{36}\text{O}_2$ (m.p. 69.6°C), are the outstanding higher fatty acids. They are produced in large quantities by the acid hydrolysis of fats and fatty oils. Both are crystalline solids, practically odorless and tasteless, non-volatile, lighter than water, and practically insoluble in it; both are readily soluble in ether, chloroform, and similar organic solvents; in short, they closely resemble the hydrocarbons of paraffin wax in their physical properties. They are used in candles and in the manufacture of a number of their salts (palmitates and stearates). When heated with sodium carbonate solutions, these acids are converted into their sodium salts, of great importance as ordinary *soap*:



11-9 Benzoic acid, $\text{C}_6\text{H}_5\text{COOH}$, is the simplest aromatic acid. It was first obtained from *gum benzoin*—whence its name. Benzoic acid is the end product of the oxidation of benzyl alcohol, benzaldehyde, benzyl chloride, toluene, and many other aromatic compounds in which a single side chain is attached to the benzene nucleus. It has been manufactured by the direct oxidation of toluene and also by chlorinating toluene to benzotrichloride and hydrolyzing the latter by boiling with water and powdered iron:

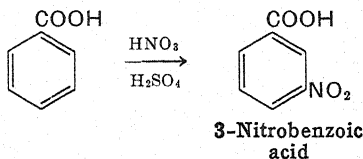


A probable intermediate here is *orthobenzoic* acid, $\text{C}_6\text{H}_5\text{C}(\text{OH})_3$. The principal industrial method now in use is the catalytic decarboxylation of phthalic acid (Sec. 24-10).

Benzoic acid is a crystalline solid (m.p. 121.7°C), sparingly soluble in cold water (2.9 grams per liter at 20°C). It dissolves readily in solutions

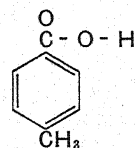
of sodium hydroxide and sodium bicarbonate, through the formation of water-soluble sodium benzoate, and is freely soluble in ether, benzene, and most other organic liquids. It is used mainly for making its salts and esters, *benzoates*. Sodium benzoate is widely used as a food preservative (*e.g.*, in fruit juices, catsups, etc.), and several esters are perfume materials.

Chemical Properties. Benzoic acid closely resembles the fatty acids in all reactions of the carboxyl group; that is, it forms salts, esters, and the other usual types of acid derivatives (Chap. 12). But, because it contains the aromatic nucleus, it also reacts in many ways like benzene. Six atoms of hydrogen are added by the Sabatier reaction, forming cyclohexanecarboxylic acid, $C_6H_{11}.COOH$. Nuclear hydrogen atoms are replaced by the usual benzene substitution reactions yielding *substituted* benzoic acids; *e.g.*,

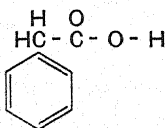


The COOH group is *meta*-directing and deactivating so that such substitutions proceed less readily than with benzene (*cf.* phenol, Sec. 8-29).

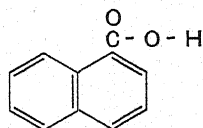
11-10 Other aromatic acids are quite numerous but require little attention since they are so similar to benzoic acid in their physical and chemical properties. All are crystalline solids (whereas the fatty acids up to C_{10} are liquids). All are practically insoluble in water but dissolve in solutions of alkalis and alkali carbonates and in most organic solvents. Examples include:



p-Toluic acid
m.p. 176.8°



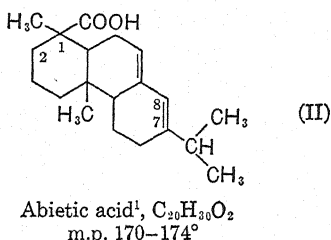
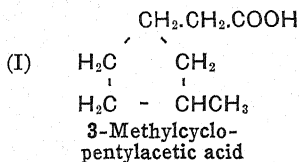
Phenylacetic acid
m.p. 76.7°



α -Naphthoic acid
m.p. 160°

Phenylacetic acid is typical of those aromatic acids in which the carboxyl group is not directly attached to the nucleus. It is manufactured from benzyl chloride by the Grignard reaction (Sec. 11-13) and by the nitrile synthesis (Sec. 12-17). Phenylacetic acid has a pleasant odor itself, and a number of its esters are prepared for use in the synthetic-perfumes industry. Its largest use is for reduction (through one of its esters) to phenylethyl alcohol, a major perfume ingredient.

11.11 Alicyclic Acids. Two types of naturally occurring acids derived from alicyclic hydrocarbons require mention. The *naphthenic* acids occur in petroleum, especially in those oils which contain a high percentage of naphthenes (cyclanes). They contain five- or six-membered rings, usually with one or more alkyl radicals attached, and a single COOH group, which may be joined directly to the ring or through a chain of CH₂ groups. A rather simple example is (I). Mixtures of naphthenic acids are obtained by agitating higher petroleum distillates with a solution of sodium hydroxide, which dissolves them out as sodium salts. They are generally used in the form of heavy-metal salts, *e.g.*, cobalt and manganese salts as driers in paints and varnishes, copper naphthenates as fungicides, and lead naphthenates in manufacturing high-pressure lubricants.



Resin acids, C₂₀H₃₀O₂, are the chief components of ordinary *rosin* from pine trees (Sec. 4.10). Boiling with glacial acetic acid converts some of these into *abietic acid*, which is thus obtained cheaply in very large quantities. Pure abietic acid is a colorless, transparent solid. It is used ordinarily in less refined form in making laundry soaps, paper sizes, etc., and for modifying alkyd resins.

11.12 Sources of Acids. As already indicated, the most important source of many carboxylic acids is in natural products where they may occur either in the free state or, more commonly, as esters or salts. Some others are produced by *fermentation* processes from the natural sugars (*e.g.*, acetic acid in vinegar and lactic acid in sour milk).

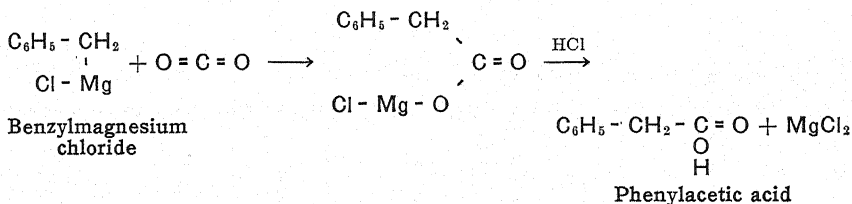
Oxidation of other organic compounds, natural or synthetic, is another important source and is a method commonly used in the laboratory. This depends on the fact that the *carboxyl group* is *highly resistant to further oxidation* (the exception of formic acid has been noted); hence when an acid is formed by a process of oxidation, it is unlikely to undergo further change. Oxidation of a primary alcohol or of an aldehyde

¹ The formulas of complex alicyclic compounds are greatly simplified by the convention used here; that is, each angle represents a carbon atom with as many attached hydrogen atoms as are necessary to satisfy any valences not shown. Thus, in abietic acid, C² has two hydrogen atoms, C⁸ has one, and C¹ and C⁷ carry none.

yields the *corresponding* acid. Most other types of compounds yield on oxidation one or more acids containing *fewer* carbon atoms; this has been illustrated in the oxidation of side chains in aromatic compounds (e.g., butylbenzene to benzoic acid) and in the oxidation cleavages of alkenes, ketones, etc.

Synthesis. Several general methods are available for preparing acids from compounds containing a *smaller* number of carbon atoms, *i.e.*, by reactions involving the formation of new carbon-to-carbon linkages. The Grignard synthesis described below and the nitrile synthesis (Sec. 12-17) are general methods in which *a carbon chain is lengthened by one atom*. Other methods which are useful in preparing a considerable variety of acids are the acetoacetic ester, malonic ester, and Perkin syntheses described in later chapters.

11-13 Grignard Synthesis of Acids. Grignard reagents add readily to a carbonyl bond of carbon dioxide, the reaction being entirely similar to that with aldehydes and ketones (Sec. 10-6). Dry carbon dioxide gas may be led into the Grignard reagent, or "dry ice" may be added. When the addition product is decomposed by dilute HCl, it yields a carboxylic acid containing one more carbon atom than the organic halide used in preparing the Grignard reagent, *e.g.*,



The wide variety of halogen compounds which form Grignard reagents makes possible the preparation of many different acids by this reaction, including some which are not obtainable by other means. This use of the Grignard reagents is sometimes called *carbonation*.

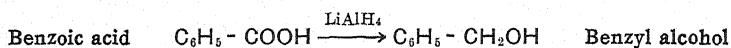
CHEMICAL PROPERTIES OF ACIDS

11-14 Acid Derivatives and Substituted Acids. The most important reactions of the organic acids, $\text{R}.\text{COOH}$, are those which involve some change in the *carboxyl group* and lead to the formation of various types of related compounds known as *acid derivatives* (salts, esters, etc.). These reactions and their products are considered in the next chapter.

Substituted acids are compounds formed from the simple carboxylic acids by any change in the *hydrocarbon radical*, R . A typical example is 3-nitrobenzoic acid (Sec. 11-9). The direct formation of such substituted

acids is most important in the aromatic series, where nuclear hydrogen atoms can be replaced by the usual methods of nitration, sulfonation, etc. Direct substitution of the fatty acids is practically limited to halogenation at the *alpha* carbon (Sec. 20·2).

11·15 Reduction; Addition Reactions. The carboxyl group is highly resistant to the addition of hydrogen. All ordinary reducing agents fail. The one important exception is lithium aluminum hydride, LiAlH_4 , described in Section 10·5. Many acids, dissolved in anhydrous ethyl ether and treated with this reagent, are reduced to the corresponding primary alcohols with yields of 80 per cent or better, *e.g.*,



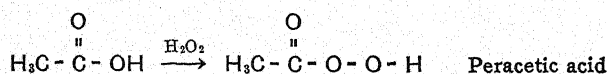
This method of direct reduction is, as yet, limited to laboratories.

Industrially, the *indirect* reduction of acids is a large-scale operation of considerable importance. The usual method is the reduction of the ester of a carboxylic acid (Secs. 12·8 and 16·22).

The carboxyl group is likewise indifferent to the many other reagents which readily add at the $\text{C}=\text{O}$ group of aldehydes and ketones. This may be attributed in part to dimerization of acids, in part to resonance, and in part to ionization, all of which tend to reduce the double-bond character of the $\text{C}=\text{O}$ component of the COOH group. These factors are absent or minimal in esters and other acid derivatives (Chap. 12) which, accordingly, add hydrogen and some other reagents more readily.

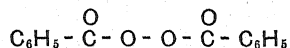
11·16 Oxidation of Acids. The resistance of carboxylic acids to oxidation by most chemical reagents has been stressed already (Sec. 11·12) and has been connected with the fact that there is no hydrogen atom on the partially oxidized carbon. The fact that acids are so often end products when other organic compounds are oxidized with nitric acid, dichromic acid, or permanganate solutions attests their indifference to these strong oxidizing agents.

Organic *peracids* are formed through the action of hydrogen peroxide, H_2O_2 . For example, hydrogen peroxide in the 30 to 90 per cent concentrations now commercially available acts on glacial acetic acid to give good yields of peracetic acid:



This reaction involves, in effect, the oxidation of oxygen. Peracetic acid, perbenzoic acid, and other peracids obtained in like manner are effective reagents for the *regulated* oxidation of alkenes to glycols (Sec.

16.4). Benzoyl peroxide, Lucidol,



is widely used as a catalyst for addition polymerizations. It is made by the action of sodium peroxide on benzoyl chloride.

11.17 Heats of Combustion. Carboxylic acids, like practically all other organic compounds, burn in air. Thus, the vapors from boiling glacial acetic acid are easily ignited, and candles are sometimes made of palmitic and stearic acids.

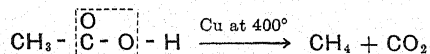
Comparison of the heat evolved on complete combustion of 1 mole of each of the following compounds brings out some significant relations:

Ethane, 30 grams	$\text{C}_2\text{H}_6 + \frac{1}{2}\text{O}_2 \longrightarrow 2\text{CO}_2 + 3\text{H}_2\text{O} + 368.4 \text{ kcal}$	>40.8 kcal
Ethanol, 46 grams	$\text{C}_2\text{H}_6\text{O} + 3\text{O}_2 \longrightarrow 2\text{CO}_2 + 3\text{H}_2\text{O} + 327.6 \text{ kcal}$	>48.6 kcal
Acetaldehyde, 44 grams	$\text{C}_2\text{H}_4\text{O} + \frac{1}{2}\text{O}_2 \longrightarrow 2\text{CO}_2 + 2\text{H}_2\text{O} + 279. \text{ kcal}$	>69.6 kcal
Acetic acid, 60 grams	$\text{C}_2\text{H}_4\text{O}_2 + 2\text{O}_2 \longrightarrow 2\text{CO}_2 + 2\text{H}_2\text{O} + 209.4 \text{ kcal}$	

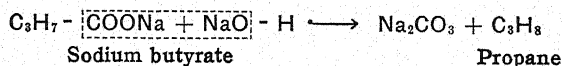
The progressive decreases in molar heats of combustion measure the heat evolved in successive stages of the oxidation of ethane. Thus the oxidation of acetaldehyde to acetic acid is exothermic to the extent of 69.6 kcal per mole.

On a *gram-for-gram* basis, another factor enters. One gram of C_2H_6 is 1 gram of combustible carbon and hydrogen; 1 gram of $\text{C}_2\text{H}_4\text{O}_2$ represents only 0.47 ($\frac{28}{60}$) gram of C and H. Hence, quite aside from the heat evolved in the oxidation of 0.47 gram of C_2H_6 to $\text{C}_2\text{H}_4\text{O}_2$, 1 gram of the latter could not give off in burning any more heat than 0.47 gram of ethane mixed with 0.53 gram of some noncombustible material. Both the factors here mentioned are involved in explaining the fact that a gram of carbohydrate food yields only 4 kcal when oxidized in the animal body, whereas the corresponding value for fats is better than 9 kcal (Sec. 27.4).

11.18 Decarboxylation. Under suitable conditions a molecule of carbon dioxide can be eliminated from a carboxylic acid, forming the next lower hydrocarbon. This amounts to the replacement of the COOH group by hydrogen, for which reason it is called decarboxylation. One method is to pass the vapors of the acid over a finely divided metallic catalyst maintained at a high temperature, *e.g.*,



A more convenient laboratory method is to heat a *salt* of the acid with soda lime ($\text{NaOH} + \text{CaO}$) *e.g.*,



Benzene and various other hydrocarbons were first obtained in this way, from salts of (their next higher) acids found in nature. The yields are poor, however, and the method has little present use as applied to monocarboxylic acids. It is important in connection with malonic and certain related dicarboxylic acids which can be decarboxylated much more easily (Sec. 19-4).

Competing reactions which can occur under similar conditions account in part for the low yields obtained in decarboxylating acids of the type $R.COOH$. Two molecules of acid can react with the elimination of H_2O to form an anhydride (Sec. 12-11). Or two molecules of acid (or salt) can react with the elimination of CO_2 and H_2O simultaneously, forming a ketone (Sec. 10-3, paragraph 1).

11-19 Detection and Identification. A compound is recognized as acidic (1) if it is insoluble in water but dissolves in dilute alkalis or (2) if it is soluble in water and this solution requires an appreciable amount of alkali for neutralization to phenolphthalein. When an organic compound is shown to be an acid by one of these tests, it becomes necessary to distinguish between carboxylic acids and other types of acidic compounds, of which sulfonic acids and phenols are the commonest. Absence of sulfur in the qualitative elementary analysis excludes sulfonic acids. Phenols are usually eliminated if the compound fails to give either the bromine-water or ferric chloride test; it is also useful to remember that water-insoluble carboxylic acids dissolve in sodium bicarbonate solutions whereas unsubstituted phenols do not.

Neutralization Equivalent. If a pure compound has been classified as a carboxylic acid, its neutralization equivalent should be determined. A weighed portion dissolved in water or neutral ethanol is titrated with a standard solution of sodium hydroxide using phenolphthalein as indicator. From the experimental results one calculates the weight of acid required to neutralize one equivalent (40.01 grams) of pure $NaOH$. The neutralization equivalent of a monobasic acid equals its molecular weight; for any other acid it equals the molecular weight divided by the number of hydrogen ions furnished by one molecule of the acid. An accurately determined neutralization equivalent, in combination with a sharp melting point, is often sufficient to identify an unknown carboxylic acid.

Derivatives for the identification of acids are described in Section 12-19.

Questions

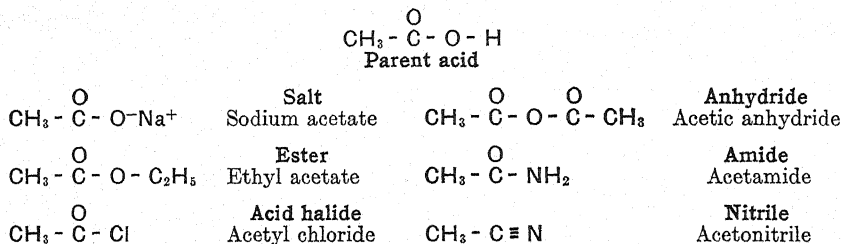
1. (a) Write the structural formulas of three branched-chain isomers of caproic acid and give their *systematic* names. (b) Write the structural formulas of isobutyric acid and of trimethylacetic acid.
2. Summarize the relations between the physical properties of acetic acid and other ethane derivatives.
3. (a) If a curve showing the boiling points of the normal fatty acids were added to Figure 8-1, describe its location. (b) Explain this location in terms of the type of molecular association exhibited by carboxylic acids.
4. Write the formulas of ethyl alcohol and acetic acid, showing all valence electrons. Use these formulas in explaining accurately *how* and *why* acetic acid acts as an acid while ethyl alcohol is a neutral compound.
5. Write the full series of reactions involved in the manufacture of acetic acid from calcium carbide.

6. In what properties, and why, does formic acid differ from all its homologues?
7. Which of the following isomeric acids would you expect to be stronger and why: $(\text{H}_3\text{C})_3\text{C}.\text{CH}_2.\text{CH}_2.\text{COOH}$ and $\text{H}_3\text{C}.\text{CH}_2.\text{CH}_2.\text{C}(\text{CH}_3)_2.\text{COOH}$.
8. What organic compounds should be expected among the stable products formed when the following compounds are refluxed with a vigorous oxidizing agent: (a) 3,4-dimethyl-2-pentene; (b) isopropyl benzene; (c) 5-methyl-2-hexanone.
9. Write structural equations for the major reactions, if any, to be expected when benzoic acid: (a) is refluxed with dichromic acid; (b) is treated with nascent hydrogen; (c) is warmed with a solution of sodium bicarbonate; (d) is passed in the form of vapor, mixed with hydrogen, over a heated nickel catalyst; (e) is mononitrated; (f) is dinitrated; (g) is converted into sodium benzoate and the dry salt, mixed with soda lime, is strongly heated; (h) is converted into sodium benzoate and the pure dry salt is strongly heated.
10. Starting with 1-hexanol, write full structural equations for the preparation of heptanoic acid by the Grignard reaction.
11. Predict how, if at all, the heat of combustion *per gram* of stearic acid would differ from that of acetic acid; explain your reasoning.
12. How could you most readily distinguish, by solubilities, between benzoic acid and a solid alcohol?
13. A sample weighing 0.2456 gram of a certain pure organic acid was dissolved in water and titrated to the phenolphthalein end point with a 0.2000 *N* solution of sodium hydroxide, 26.40 ml being required. Calculate the neutralization equivalent of this acid. What is the molecular weight of the acid if it is monobasic? Dibasic?
14. Distinguish clearly, by words and examples, between acid derivatives and substituted acids.

CHAPTER 12

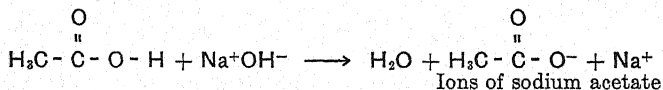
DERIVATIVES OF CARBOXYLIC ACIDS

Carboxylic acids yield six types of derivatives, namely, *salts*, *esters*, *acid halides*, *acid anhydrides*, *amides*, and *nitriles*. The structure typical of each class is illustrated by the following derivatives of acetic acid:



Most of the many other carboxylic acids are capable of yielding derivatives of all these types. Hence, such compounds are very numerous, and the chemical reactions interrelating them with the parent acids and with each other are both of theoretical interest and of practical importance.

12-1 Salts of carboxylic acids are usually prepared by neutralizing the acid, or a solution of the acid, with a base, *e.g.*,



When a solution of acetic acid is thus neutralized with sodium hydroxide, the ions of sodium acetate—a soluble, strong electrolyte—remain as such in solution. On concentration by evaporation, they may separate as ionic crystals, with or without water of hydration; sodium acetate crystallizes with three molecules of water. If the desired salt is insoluble in water, it may be prepared by reaction between solutions of two other salts; thus, silver benzoate is precipitated when neutral solutions of sodium benzoate and silver nitrate are mixed. Salts are named after their parent acids by changing the terminal *-ic* to *-ate*, *e.g.*, all salts of acetic acid are *acetates* and those of benzoic acid are *benzoates*.

It has been pointed out already that the carboxylate ions of salts are stabilized by resonance between equivalent forms [formulas (I) and (II)

of Section 11·5], which distributes the unit negative charge over the two oxygen atoms. By reason of this charge, carboxylate ions such as acetate ion, $\text{H}_3\text{C}.\text{CO}_2^-$, are nucleophilic reagents.

The physical properties of a typical salt as compared with those of its parent acid are shown in Table 12·1. It suffices to add that, as a general rule, *sodium*, *potassium*, and *ammonium* are the only common salts which are freely soluble in water; these are also the ones most commonly encountered. Salts of higher fatty acids with the heavier metals are often oil-soluble.

TABLE 12·1 COMPARATIVE PHYSICAL PROPERTIES OF A TYPICAL† CARBOXYLIC ACID AND ITS SODIUM SALT

Property	Benzoic acid	Sodium benzoate
Melting point.....	121.7°; sharp	Decomposes
Boiling point.....	249°; without change	Decomposes
Distillation.....	Volatile alone or with steam	Nonvolatile
Water solubility.....	Practically insoluble†	Freely soluble
Ether solubility.....	Freely soluble	Insoluble
Ionization.....	Low; weak electrolyte	High; strong electrolyte

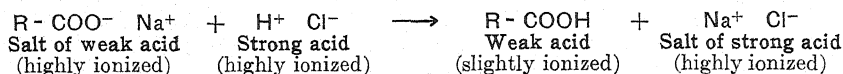
† The *lower* fatty acids, through C_4 , are miscible with water. The great majority of carboxylic acids, however, contain more than four carbon atoms and are very sparingly soluble; benzoic acid is typical of these.

Salts of the carboxylic acids generally form *ionic* crystals analogous to those of Na^+Cl^- (Fig. 1·2). Because of the sizes and shapes of the organic anions, these crystals have more complex lattices than those of sodium chloride. The strong electrical attractions between the ions of all ionic crystals explain why salts are generally nonvolatile and usually do not melt except with decomposition. But these attractions are weaker than in most common inorganic crystals; hence, salts of organic acids are generally softer and more easily deformed by pressure. The forces become weaker as the anions become larger—for example in the soaps, which are sodium salts of C_{12} to C_{18} fatty acids.

Uses. The salts of carboxylic acids find many industrial applications which depend upon their individual properties. By far the largest is the use of sodium salts of the higher fatty acids as soap. Many of these uses depend upon the greater water solubility of sodium salts as compared with their parent acids—*e.g.*, the use of sodium benzoate as a food preservative and of sodium salicylate in medicine. Salts also have advantages over acids in certain syntheses.

Conversion to Acids. It is often necessary, both in the laboratory and in industry, to convert a salt into its parent acid. The latter, being a

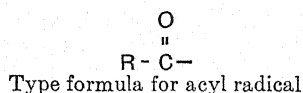
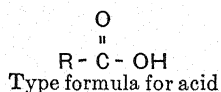
weak acid, is readily *liberated* by treatment with any stronger acid such as HCl or H₂SO₄:



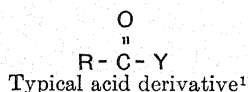
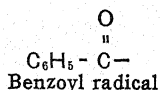
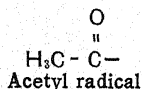
When a free organic acid has thus been liberated from a salt, the method for isolating the pure substance depends upon its specific physical properties; if it is an insoluble solid, like benzoic acid, it is filtered off; if an insoluble oil, like caproic acid, it may be removed in a separatory funnel or extracted with ether. The lower fatty acids remain dissolved when liberated from solutions of their salts and are more difficult to isolate; they are best obtained by treating the dry salt with concentrated sulfuric acid and distilling.

12-2 Organic Derivatives of Acids. The salts of carboxylic acids necessarily contain carbon and, therefore, fall within the broad definition of organic compounds. But, as has just been shown, they are electrovalent and most of their reactions are ionic. This sets the salts apart from the five classes of truly organic, covalent compounds which are derived from carboxylic acids through various changes in the COOH group—esters, acid chlorides, acid anhydrides, amides, and nitriles. Some common characteristics of these derivatives should be considered before the different classes are taken up individually.

Esters, acid chlorides, acid anhydrides, and amides all contain an *acyl radical*, which may be regarded as formed by removal of the *hydroxyl group*, OH, from a carboxylic acid:



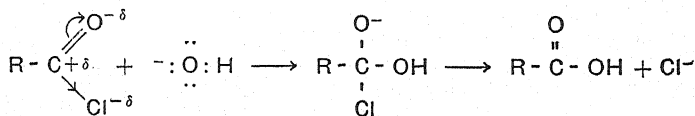
These acyl radicals are named individually from their parent acids by replacing the terminal *-ic* by *-yl*:



In each class of acid derivative (except the nitriles¹) Y is an electron-attracting atom or group, which favors the normal polarization of the C=O groups (Sec. 10-4) and helps increase the +δ charge on the carbon atom. This effect is especially marked in the acid chlorides, which are easily attacked by many nucleophilic reagents. Addition of such a

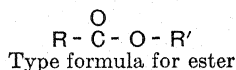
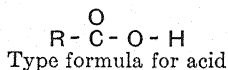
¹ The nitriles, which do not conform to this type formula, are considered separately in Section 12-16.

reagent to the carbon atom is followed immediately, or accompanied, by the release of chloride ion, *e.g.*,

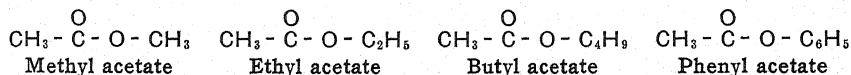


Esters, acid anhydrides, and amides react similarly but less readily with nucleophilic reagents. Usually a catalyst—an acid or a base—is needed to give practical rates of reaction.

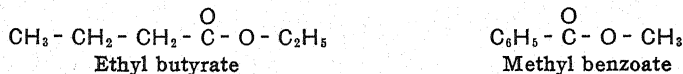
12.3 Esters of carboxylic acids are conveniently described as compounds in which an acyl radical and a hydrocarbon radical are joined through an oxygen atom (*cf.* ethers, page 165). They are *named* by thinking of them as compounds in which the COOH hydrogen atom¹ of an acid has been replaced by a hydrocarbon radical:



Each carboxylic acid may yield many different esters, depending on the nature of the hydrocarbon radical, R', *e.g.*,



Like the salts of acetic acid, the esters just shown are all known as *acetates*. Those which are related in the same way to butyric, benzoic, and other acids are described, respectively, as butyrates, benzoates, etc., *e.g.*,



General Properties and Uses. Most esters except those of very high molecular weight are colorless liquids with marked and agreeable odors. Boiling points are considerably lower than those of the carboxylic acids with which they are isomeric, indicating that they are nonassociated. Like most other oxygen-containing compounds they dissolve in cold sulfuric acid through the formation of oxonium ions or salts. Except for methyl acetate and few others of low molecular weight, esters are practically insoluble in water.

Large quantities of some esters (*e.g.*, ethyl, butyl, and amyl acetates and esters of ethylene glycol) are manufactured for use as solvents in producing lacquers, artificial leather, etc. Many others are used, in

¹ The true—and quite different—*synthetic* relationship of esters to the carboxylic acids is explained in Section 12-6.

smaller but significant amounts, in flavors and in the synthetic-perfumes industry. Two very important groups, the esters of glycerol and the esters of cellulose, are considered in later chapters.

12.4 Preparation and Manufacture. The ester linkage can be established by several general methods, the most important of which industrially is the reaction between an acid and an alcohol (*direct esterification*, below). Others include:

1. *Reaction between the salt of an acid and an alkyl halide, e.g.,*

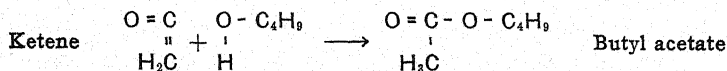


Silver salts and *alkyl iodides* give the best yields, but both are expensive. Their use is generally confined to research work in which it is important to obtain a high yield of the ester of some rare acid or alcohol. This method is especially desirable for making esters of *tertiary* alcohols and of certain acids of special structures (Sec. 22.15).

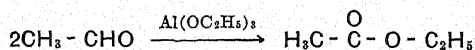
2. *Reaction between an alcohol, or a phenol, and an acid chloride.* Esterification with acetyl chloride as a distinguishing test for the lower aliphatic alcohols was described in Section 8.35. The general reaction is discussed under acylation, Section 12.10. It is frequently used in the laboratory for preparing small amounts of solid esters for the purpose of identification.

3. *Reaction between an alcohol, or a phenol, and an acid anhydride.* Phthalic anhydride and acetic anhydride are used in large quantities for manufacturing esters of their parent acids, particularly the esters of polyhydroxy compounds; the alkyd resins and cellulose acetate rayon are important products. A typical equation for esterification with acetic anhydride is given below (Sec. 12.12).

4. Esters of *acetic acid* are also obtainable by special methods. One is the reaction between ketene and an alcohol, *e.g.,*

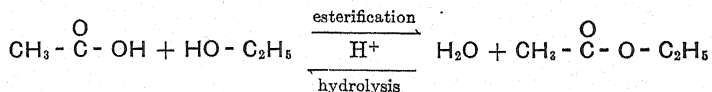


Ethyl acetate can be made by condensing two molecules of acetaldehyde with the aid of aluminum ethoxide (Tischenko reaction):



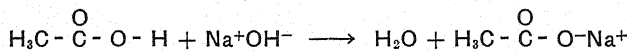
12.5 Direct Esterification. The usual method for preparing and manufacturing esters consists in refluxing together a carboxylic acid and an alcohol in the presence of a small amount of hydrochloric or sulfuric acid to furnish hydrogen ion for catalysis. Under these same conditions the reaction products—ester and water—react to form the original acid and alcohol (hydrolysis). Hence, neither reaction can go to completion

and a state of equilibrium is established, *e.g.*,



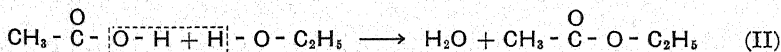
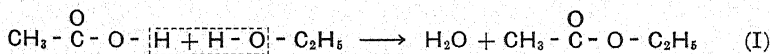
Starting with 1 mole each of ethyl alcohol and acetic acid, equilibrium is established when the system contains $\frac{2}{3}$ mole each of ethyl acetate and water and $\frac{1}{3}$ mole each of acetic acid and alcohol. The maximum yield under these conditions is therefore only two-thirds of the theoretical. With other acids and alcohols both the rate of esterification and the position of equilibrium are influenced by the structures of the reactants. For example, tertiary alcohols and acids of the type $\text{R}_3\text{C.COOH}$ are esterified extremely slowly. It is customary to improve yields by some method which shifts the equilibrium toward the right. This can be done by using a large excess of the cheaper reagent, by conducting the reaction in a column still (industrial method) from which a low-boiling ester can be removed as formed, or by any method for the removal of water.

12-6 Mechanism of Esterification. The formation of an ester by elimination of water between an acid and an alcohol bears a formal resemblance to the neutralization of an acid by an inorganic base, *e.g.*,



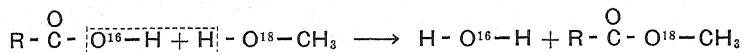
Actually, these reactions differ in many essentials. Neutralization is an *ionic* reaction that goes to completion through the union of hydrogen and hydroxyl ions to form slightly ionized water. Like most other ionic reactions in solution, it is practically instantaneous at any temperature. Esterification never goes to completion, and equilibrium is attained only after a considerable lapse of time; years are required at room temperature in the absence of added hydrogen ion for catalysis; even at the refluxing temperature and with a catalyst, some hours may be necessary. These facts point clearly to different mechanisms for esterification and neutralization.

The net result of esterification is the elimination of a molecule of water between the hydroxyl group of an alcohol and the carboxyl group of an acid. This might occur in either of the following ways:

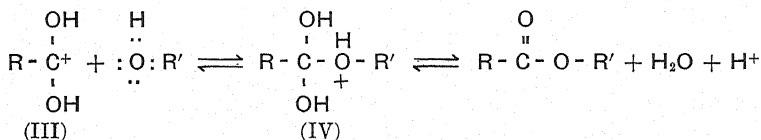


Since both these reactions should yield the same product, the structure of the latter gives no clue as to whether the hydroxyl group is eliminated

from the alcohol (I) or from the acid (II). There is, however, much evidence that the *hydroxyl group is eliminated from the acid*. The most direct proof was obtained by esterifying an organic acid with methyl alcohol containing a high percentage of the "heavy" oxygen (O^{18}) isotope. The water formed in the reaction had the normal density—which could be true only if its oxygen came from the acid, as indicated in (II) and as follows:



It now appears that the initial step in esterification is addition of a proton from the catalyst to oxygen of the carboxylic acid, giving (III). Addition of a molecule of alcohol gives (IV), from which the ester is formed by elimination of a proton and a molecule of water:



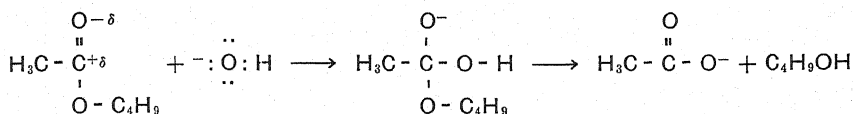
This explains the catalytic action of the added inorganic acid and why the oxygen eliminated in the water cannot come from the alcohol. All stages are reversible, and reaction toward the left represents the acid-catalyzed hydrolysis of esters.

Alcoholysis. If the ester $R.COO.R'$ is heated with a large excess of the alcohol $R''OH$ in the presence of a mineral acid (or of a *small* amount of an alkoxide), it may be converted largely into the ester $R.COO.R''$. As the original ester is hydrolyzed, it forms $R.COOH$ and $R'OH$. In the reverse reaction, which proceeds under the same conditions, the acid may react either with $R'OH$ or with $R''OH$ and, because the latter is in excess, the product will be mainly $R.COO.R''$. By analogy to hydrolysis, this reaction is described as *alcoholysis* or, sometimes, as *transesterification*.

12-7 Saponification. The most important reaction of esters is *alkaline* hydrolysis, commonly called saponification. This is effected by boiling under reflux with a solution containing more than an equivalent of a base such as sodium hydroxide. The reaction is irreversible, and the ester is converted quantitatively into the alcohol and a salt of the acid from which it was derived, *e.g.*,



This occurs through a nucleophilic attack by hydroxide ion on the $+\delta$ carbonyl carbon, followed or accompanied by the elimination of a molecule of alcohol:

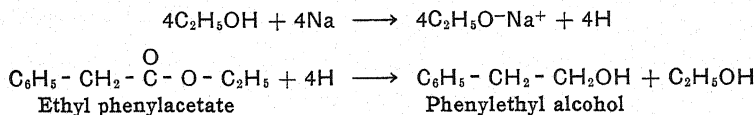


Saponification of the natural fats and fatty oils is conducted on a very large industrial scale for the manufacture of soap and glycerol (Sec. 16-19).

The *saponification equivalent* of an ester is the weight of it which will consume in hydrolysis 1 gram equivalent of a base, *e.g.*, 40.01 grams of NaOH. This constant is of considerable value in the identification of esters. It is determined by refluxing a weighed sample of ester with a measured volume of standard alkali solution estimated to be in excess; when reaction is complete, the amount of alkali consumed in hydrolysis is found by titrating the excess with a standardized acid. The saponification equivalent is then calculated by direct proportion. For an ester of a monocarboxylic acid with a monohydric alcohol, the saponification equivalent is equal to the molecular weight.

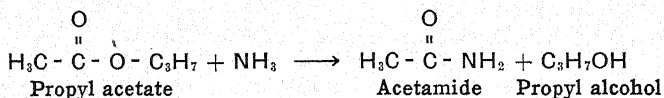
12-8 Other Ester Reactions. Besides saponification, esters enter into various other reactions, the most noteworthy of which are the following.

Reduction; Bouveault-Blanc Reaction. When an ester is treated with active hydrogen, its acyl radical is reduced and yields the corresponding primary alcohol. The action of sodium on an alcohol used as a solvent for the ester—the Bouveault-Blanc reaction—is the most effective industrial source¹ of active hydrogen. This is, in effect, an indirect method for reducing R.COOH to R.CH₂OH and is especially useful because the direct reduction of an acid is seldom feasible (Sec. 11-15). The manufacture of phenylethyl alcohol for the synthetic-perfumes industry affords an example. Phenylacetic acid is esterified with excess of ethyl alcohol and the product treated with metallic sodium:



Its much higher boiling point (219 to 221°C) makes it possible to separate phenylethyl alcohol from the "reducing alcohol," ethanol. The Bouveault-Blanc reaction is described in more detail in Section 16-22 in connection with one of its major applications.

Ammonolysis. When an ester stands with concentrated aqueous ammonia, it is slowly converted into an amide and an alcohol, *e.g.*,

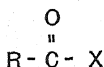


¹ Lithium aluminum hydride gives excellent results in the laboratory.

This reaction is analogous to alkaline hydrolysis and proceeds through a nucleophilic attack by ammonia on the $+\delta$ carbon of the ester.

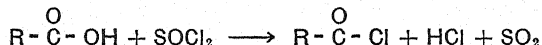
Ester Condensations. Esters enter into various condensations such as the Claisen reaction (Sec. 20-18). In these reactions the ester functions as molecule B in the scheme on page 184 because an *alpha* hydrogen atom of its acyl radical is sufficiently active to be removed by an alkaline catalyst.

12-9 Acid halides, or acyl halides, are compounds corresponding to the type formula



in which X may represent an atom of chlorine, bromine, or iodine. The acid bromides and iodides are (in this order) much less reactive than the chlorides,¹ which alone require description.

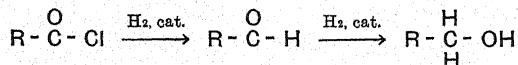
Acid chlorides are prepared by heating an acid with a chloride of a negative element, sulfur or phosphorus. *Thionyl chloride*, SOCl_2 (b.p. 78.8°C) is especially useful, if only a moderate temperature is required for reaction, since the by-products are gaseous and easily removed:



If the reaction proceeds less readily and higher temperatures are necessary, it is customary to use phosphorus pentachloride. It should be noted that the hydrogen halides, which are used so commonly to replace the *alcoholic* hydroxyl group by a halogen atom, do not effect this replacement in carboxylic acids.

12-10 Chemical Properties. The use of acid chlorides in the Friedel-Crafts synthesis of aryl ketones has been described (Sec. 10-18). Other important reactions include the following.

Rosenmund Reduction. Acid chlorides are readily reduced by catalytic hydrogenation:

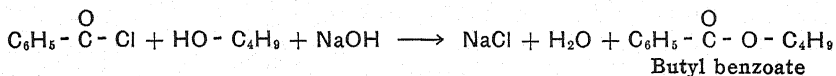


Most catalysts carry reaction on to the alcohol, although the second stage proceeds less readily than the first. The Rosenmund method gives good yields of *aldehydes*. By adding a small amount of a sulfur compound, the catalyst (palladium on barium sulfate) is poisoned sufficiently to destroy its activity in the second reaction without greatly retarding the first. The reaction can be effected by passing hydrogen into a hot

¹ Compare with the order of reactivity of Cl, Br, and I in the alkyl halides (Sec. 7-7) and offer an explanation.

benzene or toluene solution of the acid chloride, in which the catalyst is suspended.

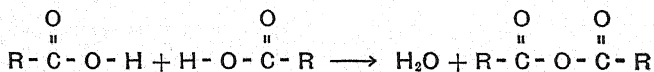
Acylation. Acid chlorides react with compounds containing active hydrogen atoms—alcohols, phenols, water, primary and secondary amines (Sec. 13·12), and ammonia. In all these reactions with organic compounds the chlorine atom is lost as chloride ion and the acyl radical is substituted for hydrogen in the other molecule. Such reactions are called *acylations*, and acid chlorides (and acid anhydrides) are *acylating agents*. A typical example is the esterification of an alcohol or a phenol by shaking with benzoyl chloride in the presence of sodium hydroxide solution (Schotten-Baumann reaction¹), *e.g.*,



It is convenient and sufficient for most purposes to represent the reactions of acid chlorides by over-all equations such as that just given. They doubtless proceed through an attack on the $+\delta$ carbon atom by a nucleophilic reagent, as was illustrated in Section 12·2 for the reaction with hydroxyl ion.

Hydrolysis vs. Ammonolysis. Acetyl chloride and a few others of low molecular weight fume in moist air and react violently, with evolution of HCl, when added to cold water. Because this tendency toward hydrolysis is so strong, these acid chlorides give only ammonium salts when added (with caution!) to aqueous ammonia. But with the higher acid chlorides, and particularly those derived from aromatic acids, ammonolysis is more rapid and good yields of amides can be obtained by shaking with concentrated "28 per cent" ammonia (Sec. 12·13).

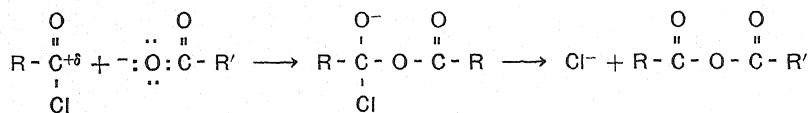
12·11 Acid anhydrides are compounds in which two acyl radicals are joined by an oxygen atom. They may be considered as formed by the elimination of a molecule of water between two carboxyl groups²:



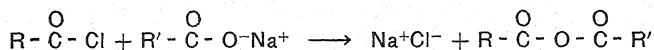
¹ The widely used method of benzoylating alcohols, phenols, and amines by shaking with benzoyl chloride in the presence of a solution of sodium hydroxide is called the *Schotten-Baumann reaction*. A similar procedure may be used with substituted benzoyl chlorides (*e.g.*, *p*-nitrobenzoyl chloride) and with benzenesulfonyl chloride (Sec. 14·5). In a modern variation, sodium hydroxide is replaced by pyridine (a tertiary organic base, Sec. 26·1). A base neutralizes the HCl, which is always a reaction product, and increases the rate of reaction.

² This type of reaction occurs readily between two COOH groups of the *same* molecule in certain dicarboxylic acids (Secs. 19·5 and 24·10), where it results in the formation of important cyclic anhydrides.

The most general method for actual preparation consists in heating a salt with an acid chloride. If these two compounds are derived from different acids, a *mixed* anhydride is obtained:

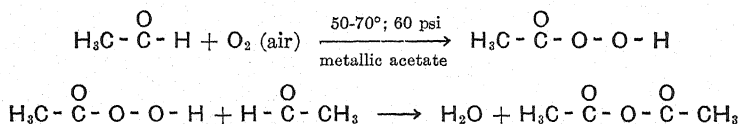


or, over-all:



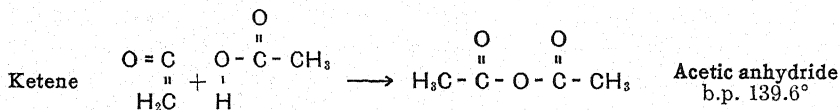
12.12 Acetic anhydride is the one aliphatic anhydride of outstanding importance (cf. phthalic anhydride, Sec. 24.10). It is produced in large quantities¹ by several special methods, each of which may under certain conditions offer a slight advantage in cost.

One of the major methods is the catalytic oxidation of acetaldehyde with air, peracetic acid being formed as an intermediate:



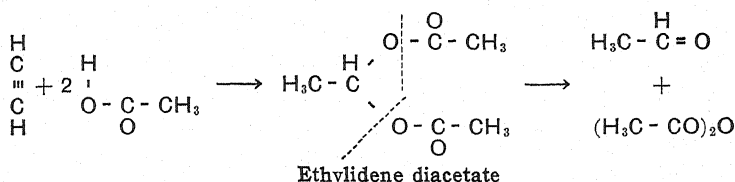
The reaction is conducted in the presence of glacial acetic acid.

Another method is based on the addition reaction between ketene (Sec. 10.15) and glacial acetic acid:

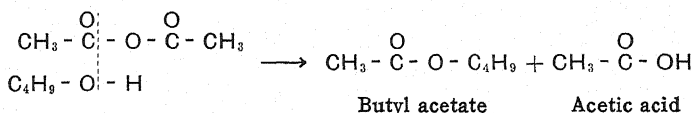


The third industrial method involves the addition of two molecules of glacial acetic acid to acetylene. This reaction is catalyzed by mercury salts, as is the hydration of acetylene to acetaldehyde. The product is ethylidene diacetate which, when distilled with zinc chloride or other anhydrous salt, yields acetaldehyde and acetic anhydride:

¹ Production of acetic anhydride (USA, 1950) amounted to 900 million pounds, the largest quantity published by the Tariff Commission for any synthetic chemical. The former method of production from sodium acetate and acetyl chloride is long since obsolete on account of its cost; this is largely true also of a modification in which sodium acetate is heated with sulfur dichloride, SCl₂, and chlorine.



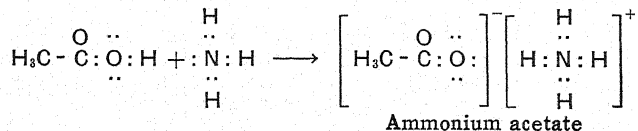
Properties and Uses. Acetic anhydride reacts like acetyl chloride, though less vigorously, with hydroxyl and amino compounds. Its one major use is for introducing acetyl radicals into other organic molecules, *acetylation*. At least three-fourths of the production goes into the manufacture of cellulose acetate (Sec. 18·24); the conversion of salicylic acid into acetylsalicylic acid, Aspirin, involves the same type of reaction. Using a simple alcohol as an example, the acetylation of a hydroxyl compound proceeds, effectively, as follows:



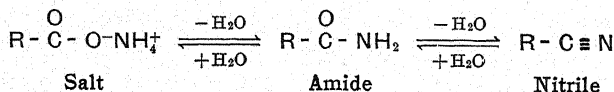
This equation illustrates the important point that only *one* acetyl group of the anhydride is utilized in an acetylation. The other acetyl group appears as acetic acid which, in all large-scale operations, is recovered by some suitable procedure.

Acetic anhydride is used instead of acetyl chloride for all industrial acetylations; it is cheaper, has a higher boiling point, and is less readily hydrolyzed by contact with moist air. Acetic anhydride is practically insoluble in cold water but, on standing, slowly passes into solution as it is converted into acetic acid. It is rapidly and completely hydrolyzed by boiling water and by hot alkaline solutions.

12·13 Ammonium Salts; Amides; Nitriles. Like all other acids, carboxylic acids react promptly with ammonia to form ammonium salts, *e.g.*,



When a dry ammonium salt is heated, a molecule of water is split out forming an amide. Strong dehydrating agents (*e.g.*, phosphoric anhydride) can eliminate another molecule of water and form a nitrile:



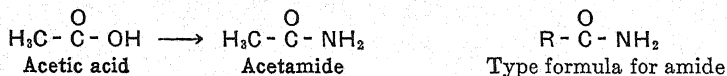
Industrially, ammonium salts are dehydrated to nitriles in a single catalytic operation (Secs. 13-8 and 19-7). The dehydration reaction can be reversed by boiling a nitrile or an amide with water containing either an acid or a base. This is a step in the nitrile synthesis of carboxylic acids (Sec. 12-17).

Reactions of Ammonia. Ammonia, NH_3 , is a colorless gas (b.p. -33.4°C) of strong and familiar odor. It is liquefied by pressure and transported thus, in steel cylinders, for use as an industrial refrigerant and in chemical industry and research. This is known as *liquid ammonia* or *anhydrous ammonia*. For ordinary laboratory purposes, ammonia is shipped as a water solution (*d*, 0.90) containing 28 per cent by weight of the dissolved gas. This solution is variously referred to as concentrated ammonia, aqueous ammonia, ammonia water, and ammonium hydroxide.

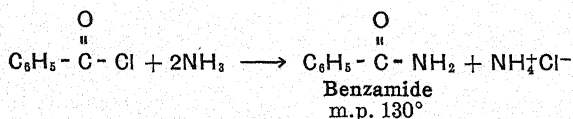
No such substance as *ammonium hydroxide*, NH_4OH , has ever been isolated. Perhaps it exists in solution as a hydrogen-bonded complex of NH_3 with H_2O . The student of organic chemistry is urgently advised to *forget* "ammonium hydroxide" and to stop thinking and speaking in terms of it (regardless of what the label on the bottle may say!). All the reactions of ammonia—both the anhydrous liquid and water solutions—are interpreted most simply in terms of the behavior of simple NH_3 molecules; they involve addition of a proton or some electron-deficient group to the unshared electron pair on the nitrogen atom. This was illustrated above in the equation for the formation of ammonium acetate.

The point of view here expressed will be found especially useful in studying the amines (Chap. 13).

12-14 Amides are compounds that may be regarded as derived from carboxylic acids by replacing the hydroxyl of the COOH by the *amino group*, NH_2 , *e.g.*,



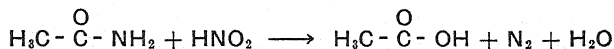
They may be regarded also as *compounds derived from ammonia* by replacing one hydrogen atom by an *acyl radical*. Both points of view are illustrated by the most general method of preparation, in which an acid halide is shaken with concentrated aqueous ammonia, *e.g.*,



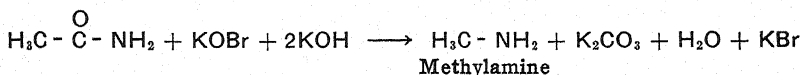
Amides have exceptionally high boiling points and with very few exceptions are crystalline solids with melting points considerably higher than those of their parent acids (*e.g.*, acetamide, with a molecular weight of only 59, melts at 82°C and boils at 221°C). These properties indicate association through strong hydrogen bonds. Only acetamide and a few others of low molecular weight are soluble in water. Solubility is no

greater in dilute acids and alkalis, showing that they are essentially neutral compounds—an important contrast with the *amines* described in the next chapter.

As already stated, amides can be dehydrated to nitriles and are readily hydrolyzed by hot dilute acids to their corresponding carboxylic acids. They react with nitrous acid, liberating nitrogen quantitatively, according to equations such as

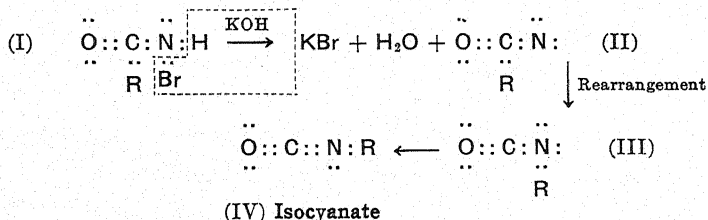


12.15 Hofmann Reaction. An amide can be converted into the next *lower* primary amine (a compound of the type R.NH_2) by warming with a strongly alkaline solution of a hypohalite. The over-all reaction is expressed by equations of the type



The Hofmann reaction, thus illustrated, is a useful *general method for shortening a carbon chain by one atom*.

Initially, the hypohalite converts the amide into an *N*-halogen¹ derivative (I), which can be isolated. When this is heated with an alkaline solution, the elements of HBr are eliminated, apparently giving a short-lived intermediate (II) in which the nitrogen atom is left with only six electrons. Nitrogen is more electronegative than carbon and regains an octet by appropriating a pair of carbon electrons—which carry with them the group *R*. Thus (III) is formed and passes by a slight redistribution of the nitrogen electrons into (IV), an isocyanate.



Isocyanates can often be isolated in the Hofmann reaction. They are well-known compounds which react readily with alkalis to give primary amines,² *e.g.*,

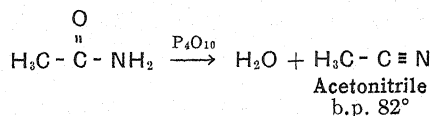


¹ The prefix *N* indicates that the atom or group named immediately after it is joined directly to a *nitrogen* atom.

² See footnote 1, page 232.

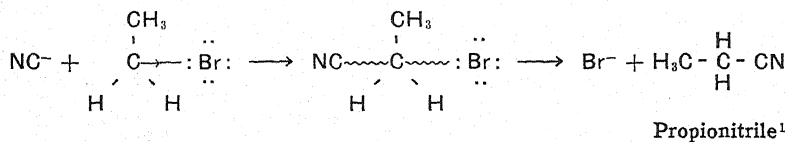
The interesting and unusual step in the sequence is the shift of the group R from one atom to another (from C to N), which constitutes a *molecular rearrangement* (cf. Sec. 16·9).

12·16 Nitriles can be made from amides by heating with a strong dehydrating agent, *e.g.*,



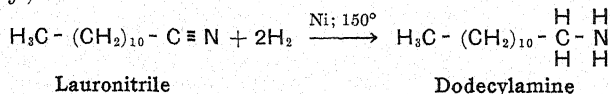
It was noted above that nitriles are produced industrially by a single-stage catalytic dehydration of ammonium salts of the corresponding acids.¹

Nitriles are commonly prepared in the laboratory from compounds containing *one less* carbon atom. Thus, they are obtained in good yields when an *alkyl* halide in alcoholic solution is heated with sodium cyanide. The cyanide ion, CN^- , or $(:\text{C}::\text{N}:)^-$, displaces halogen through a nucleophilic attack on carbon:



Benzyl chloride reacts in like manner, but chlorobenzene and other simple *aryl* halides are not reactive enough to exchange halogen in this way. The best way to attach the CN group to an aryl nucleus is through the diazo reaction (Sec. 13·17). Dry distillation of a sodium sulfonate with sodium cyanide (Sec. 14·3) is sometimes used but gives poorer yields. In each of these methods, a new carbon-to-carbon bond is formed.

Reduction. Nitriles are reduced industrially to *primary amines* (Chap. 13) by catalytic hydrogenation over Raney nickel using hydrogen at 200 psi, *e.g.*,



Thus, four hydrogen atoms are added to the $\text{C} \equiv \text{N}$ triple bond, as they add to the $\text{C} \equiv \text{C}$ triple bond of acetylene. The reduction of nitriles to primary amines is effected in the laboratory with the aid of lithium

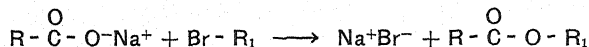
¹ The nitriles are named from the acids containing the same number of carbon atoms, which they yield on hydrolysis. In the older literature they are called *cyanides* and named after the alkyl radical to which the CN group is attached (*e.g.*, $\text{C}_2\text{H}_5\text{CN}$, ethyl cyanide).

12-19 Derivatives for Identification. Acid derivatives of all classes are readily converted into their parent acids by hydrolysis or other simple reaction. If this acid is a solid, its melting point may suffice for final identification. In the more general case, an unknown acid examined as such or obtained from another compound is converted into a solid derivative as follows:

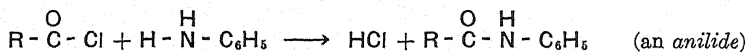
Esters. The alkyl and even the phenyl esters of many acids are liquids, but solid esters can usually be obtained by heating the sodium salt of an acid with one of the following:

<i>p</i> -Nitrobenzyl bromide.....	$\text{NO}_2\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{Br}$
Phenacyl bromide.....	$\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_2\cdot\text{Br}$
<i>p</i> -Bromophenacyl bromide.....	$\text{Br}\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{CH}_2\cdot\text{Br}$
<i>p</i> -Phenylphenacyl bromide.....	$\text{C}_6\text{H}_5\cdot\text{C}_6\text{H}_4\cdot\text{CO}\cdot\text{CH}_2\cdot\text{Br}$

All these react according to the general scheme



Amides, Anilides, and Toluides. In order to prepare these derivatives, the acid is converted into its acid chloride by treatment with thionyl chloride or a phosphorus chloride. The acid chloride is then reacted with ammonia, or aniline ($\text{C}_6\text{H}_5\cdot\text{NH}_2$), or *p*-toluidine ($\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{NH}_2$). With each of these, the essential reaction (Sec. 13-12) is the same, *e.g.*,



Questions

1. Compare the physical properties of a typical carboxylic acid with those of its sodium salt.
2. (a) Write equations for the reactions that occur when dilute sulfuric acid is added to solutions of sodium benzoate, sodium caproate, and sodium acetate. (b) From the properties of the organic products, describe the physical changes, if any, which would be observed when these reactions occur. (c) Outline a procedure for obtaining *pure* the organic product of each reaction.
3. (a) Write the structural formulas of butyl acetate and ethyl butyrate. What relation, if any, exists between these two compounds? (b) Write the structural formulas and give the names of four esters isomeric with *n*-butyric acid. (c) Write the structural formulas of one ester and three acids isomeric with methyl benzoate.
4. (a) Write the structural formulas of the following esters used in the perfume industry: phenyl acetate, benzyl acetate, *p*-cresyl acetate, *p*-methylbenzyl acetate, phenylethyl acetate, benzyl benzoate, benzyl phenylacetate, phenylethyl phenylacetate. (b) Point out any isomers among these compounds.
5. Having available any desired materials and reagents, write equations for the preparation of *n*-butyl *n*-butyrate by three methods.
6. Give evidence to show that in direct esterification of a carboxylic acid the hydroxyl eliminated comes from the acid and hydrogen from the alcohol.
7. Assuming the mechanism of esterification outlined in Section 12-6, explain the acid hydrolysis of esters and transesterification, and show why both are incomplete.
8. Offer an explanation of the fact that the direct esterification of a tertiary alcohol is a much slower reaction than that of an isomeric primary alcohol (cf. Sec. 8-7).
9. Explain the saponification of esters as a nucleophilic displacement.

10. Which ester of each of the following pairs has the higher saponification equivalent and why? (a) Ethyl benzoate and *n*-butyl benzoate. (b) Butyl acetate and ethyl butyrate. (c) Ethyl acetate and ethyl butyrate.

11. What relation is there, if any, between the numerical values of the saponification equivalent of ethyl butyrate and the neutralization equivalent of butyric acid? Explain.

12. (a) Given butanol and no other organic reagent, show how to prepare *n*-butyl butyrate. (b) Given only ethyl acetate and inorganic reagents, show how to prepare a butyl acetate. (c) Given ethyl benzoate, show how to obtain benzyl alcohol.

13. (a) Write structural equations for the action of phosphorus trichloride on ethyl alcohol and on acetic acid, pointing out the similarity. (b) What is the structural relation between an acid halide and the corresponding aldehyde? The corresponding alkyl halide?

14. Write structural equations for the principal reactions, if any, to be expected if benzoyl chloride is: (a) shaken with concentrated ammonia; (b) shaken with butanol and a solution of sodium hydroxide; (c) treated with hydrogen by the Rosenmund method; (d) treated with toluene in the presence of anhydrous AlCl_3 .

15. (a) Anhydrous ethyl ether is a useful solvent for acetyl chloride in chemical syntheses, but absolute ethanol is worthless for this purpose; explain. (b) State how and explain why the products obtained when acetyl chloride is added to concentrated ammonia differ from those obtained with benzoyl chloride. (c) How is acetyl chloride used in the laboratory as a reagent for detecting the lower aliphatic alcohols?

16. Define the term anhydride as used in inorganic chemistry and show that acetic anhydride is related to acetic acid in the same way nitric anhydride, N_2O_5 , is related to nitric acid.

17. (a) Write equations for two industrial methods for making acetic anhydride. (b) Show how ketene is used also for making esters.

18. Write structural equations for the reaction, if any, of acetic anhydride with: (a) water; (b) ammonia; (c) benzyl alcohol; (d) *p*-cresol; (e) β -naphthol.

19. Show how it is possible to convert *n*-butyric acid into butanol: (a) through ethyl *n*-butyrate; (b) through butyryl chloride; (c) directly.

20. Write the structural formulas of a typical ether, ester, and anhydride and describe each in terms of the types of radicals (alkyl or acyl) joined by the oxygen atom.

21. What type of compound is formed by the elimination of a molecule of water between: (a) two carboxyl groups; (b) two (phenolic or alcoholic) hydroxyl groups; (c) a carboxyl group and a (phenolic or alcoholic) hydroxyl group?

22. Show by structural equations the similarities and express in words the differences between the following reactions: (a) the preparation of ethers by the Williamson synthesis; (b) the preparation of esters by reaction between an alkyl halide and the salt of an acid; (c) the preparation of anhydrides by reaction between the salt of a carboxylic acid and an acid chloride.

23. Write equations for the reactions, if any, which occur when typical ethers, esters, and anhydrides are refluxed with dilute sodium hydroxide solution.

24. Describe the observations to be expected if a solution of ammonium benzoate is treated with: (a) dilute hydrochloric acid; (b) warm dilute sodium hydroxide solution.

25. Define amides: (a) as derivatives of carboxylic acids; (b) as derivatives of ammonia.

26. Write structural equations illustrating the two most general methods for the preparation of amides.

27. The physical properties of acetamide suggest that it is associated through relatively strong hydrogen bonds. Write an electron formula showing the probable mode of association.

28. Write over-all equations for the reactions, if any, to be expected if butyramide is: (a) treated with nitrous acid; (b) treated with strong alkali and sodium hypochlorite; (c) heated with phosphoric anhydride; (d) boiled with dilute sulfuric acid; (e) boiled with dilute sodium hydroxide.

29. Using the nitrile synthesis, write structural equations for all the reactions necessary in preparing: (a) *n*-butyric acid from *n*-propyl bromide; (b) *p*-toluic acid, $\text{H}_3\text{C}\cdot\text{C}_6\text{H}_4\cdot\text{COOH}$, from *p*-toluenesulfonic acid; (c) propionic acid from ethyl alcohol; (d) isobutyric acid from acetone.

30. Write structural equations for two reactions of nitriles that are analogous to reactions of acetylene.

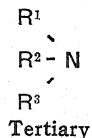
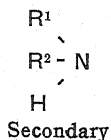
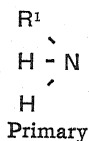
31. The following compounds in separate vessels are refluxed with an excess of sodium hydroxide solution until reaction, if any, is complete; assume efficient condensers which prevent the escape of any substance during this operation. Each condenser is then set for distillation, and steam is passed into the strongly alkaline solutions. Aside from water, what substances if any will be found in the condensed distillate from each flask? (a) Benzoyl chloride; (b) ethyl butyrate; (c) ethyl ether; (d) acetic anhydride; (e) diethyl ketone; (f) propionamide; (g) acetonitrile. *Suggestion:* Consider whether any reaction will occur and, if so, the products it will yield and how these will be affected by the excess alkali present; then consider what *volatile* substances can be present—either reaction products or original compounds which are not hydrolyzed by hot alkaline solutions.

32. A compound dissolved freely in water to give a practically neutral solution. On addition of dilute acid (HCl , HNO_3 , or H_2SO_4) there occurred an immediate separation of colorless crystals. These were shown to be organic and readily soluble in alkali. What was the probable nature of the precipitate? Of the original compound?

CHAPTER 13

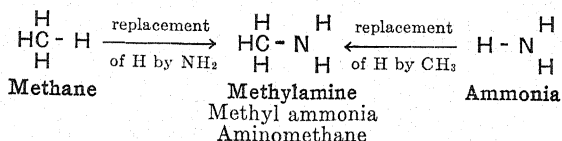
AMINES; ORGANIC BASES

Amines are compounds that may be regarded as derived from ammonia, NH_3 , by replacing one or more hydrogen atoms by as many *hydrocarbon* radicals. They are classified as *primary*, *secondary*, and *tertiary*¹ amines, according to the number of these radicals attached to the nitrogen atom. All can be represented by the type formulas:



in which R^1 , R^2 , and R^3 may stand for *any* hydrocarbon radicals, the same or different, cyclic or aliphatic.

13.1 Alkyl Amines. Methylamine is related to *ammonia* and methane as is methyl alcohol to *water* and methane (Sec. 8-3):



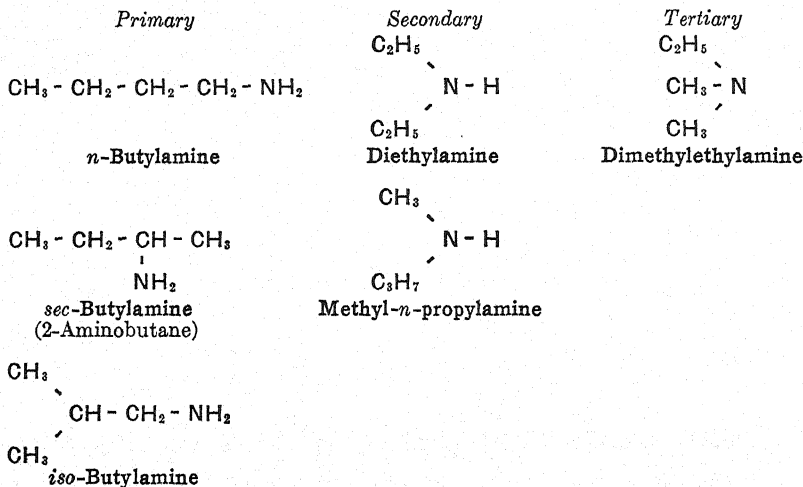
Like both parent substances, methylamine is a colorless gas (b.p. -6.5°C) under ordinary conditions. It resembles methane in being combustible, but in all other properties, including odor and high solubility in water, it is very similar to ammonia.

Methylamine is the simplest member of the homologous series of *primary* alkyl amines of the type R.NH_2 , where R may stand for any alkyl radical. As in other series, physical properties change progressively and somewhat regularly with the increasing length of the hydrocarbon chain. The lower members are either gases or low-boiling liquids, freely

¹ It is important to note the exact meaning of the terms *primary*, *secondary*, and *tertiary*, as applied to amines. This differs from the usage of the same words in connection with carbon atoms, alkyl halides, and alcohols. For example, the compound represented by the formula $(\text{CH}_3)_3\text{C.NH}_2$ is a *primary* amine although the nitrogen atom is attached to a *tertiary* carbon atom.

soluble in water and somewhat resembling ammonia in odor.¹ The highest alkyl amines are colorless odorless solids, practically insoluble in water, but dissolving in organic solvents *and in acids*. All are lighter than water.

Secondary and tertiary alkyl amines resemble physically the primary amines with which they are isomeric, though chain branching is accompanied by some lowering of boiling points. Opportunities for isomerism, and the nomenclature, are illustrated by the following amines of the formula $C_4H_{11}N$:

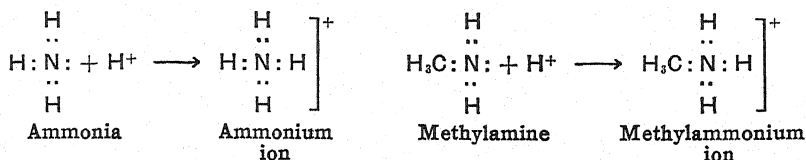


Chemical Properties. The hydrocarbon radicals in the alkyl amines are unreactive as in the parent alkanes; hence, most chemical reactions are those of the nitrogen atom or of the *N*-hydrogen atoms. The most important are: the ability to form salts with acids and otherwise act as bases; alkylation; and behavior with nitrous acid. The carbon-nitrogen linkage in an amine is *not split by hydrolysis*, an important distinction from the amides.

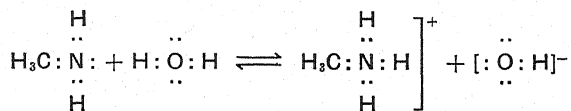
13.2 Organic Bases. The alkyl amines resemble ammonia by giving alkaline solutions when they dissolve in water and by neutralizing acids to form salts. In other words, amines are *bases*. They differ in this respect from all the classes of organic compounds previously described.

¹ Ethylamine was the first known alkyl amine, having been prepared by Adolph Wurtz in 1848 by heating ethyl isocyanate with an alkali. So closely does it resemble ammonia in odor and in other physical and chemical properties that Wurtz did not realize he had prepared a new organic compound until he accidentally made the observation that it burned.

This property is associated with the unshared electron pair on the nitrogen atom of ammonia and every amine. Through these electrons they are able to bind protons and form *ammonium* ions and *substituted-ammonium* ions, respectively, e.g.,



For each proton thus captured from water, one hydroxide ion remains:



Hence a water solution of an amine is *alkaline*, to an extent which depends on the position of this equilibrium. In a 0.1 *M* solution of ammonia in water, equilibrium is established when one molecule in about 100 has been converted into ammonium ion. The corresponding value for most alkyl amines is about five in 100, showing that they are somewhat stronger bases.

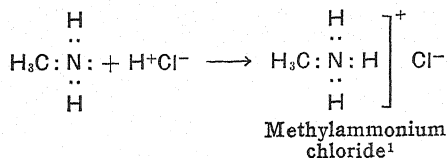
The *strength* of an amine as a base—that is, its proton-binding capacity—depends on the availability of the unshared electron pair. This depends, in turn, upon the nature of the atoms and groups attached to the nitrogen atom. The greater strength of the alkyl amines in comparison with ammonia is in keeping with the previously noted fact that alkyl groups are more electron-releasing than hydrogen. The very different situation in the aryl amines is described in Section 13.11.

Ionization Constants of Bases. The strength of weak bases is ordinarily compared, as for weak acids, in terms of their ionization constants. These are calculated by inserting experimentally determined data into equations of the type

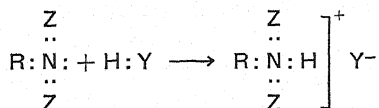
$$\frac{(\text{CH}_3\text{NH}_2^+) \times (\text{OH}^-)}{(\text{CH}_3\text{NH}_2)} = K_b$$

For methylamine $K_b = 4 \times 10^{-4}$ and for ammonia $K_b = 10^{-5}$.

13.3 Amine Salts. When methylamine is led into a solution of an acid such as hydrochloric, the gas is absorbed and on evaporation of the solution there is left a crystalline salt:

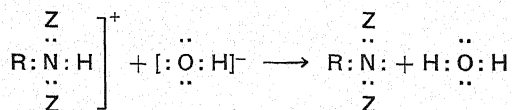


This behavior is, of course, entirely similar to that of the parent ammonia which, under like conditions, yields the familiar salt ammonium chloride, NH_4^+Cl^- . Using the type formula RZ_2N (in which Z may stand either for H or for a radical) to represent *any* amine, and HY to represent *any* acid, the general equation for salt formation becomes



The amine salts of the ordinary inorganic acids and of simple organic acids are colorless, odorless, crystalline solids which are freely soluble in water. Salt formation explains the important observation that water-insoluble higher amines dissolve readily in acid solutions. The usual test for compounds with basic properties depends on this fact. The salts differ further from their parent amines in that they are nonvolatile, are insoluble in ether and similar solvents, and are strong electrolytes. Many have definite, though quite high, melting points. The amine salts with sulfuric acid are usually acid sulfates of the type $\text{RNH}_3^+.\text{HSO}_4^-$. Most amines also form *sparingly* soluble salts with certain more complex acids both inorganic and organic (*e.g.*, chloroplatinic acid, picric acid). Such salts are sometimes prepared as derivatives in the identification of amines.

Liberation of Amines. When an amine salt is treated with a solution of a strong base such as sodium hydroxide, the amine is liberated. (Alternatively, the dry amine salt may be mixed with lime and heated.) This is explained by the fact that hydroxide ion—a very strong base—withdraws protons from substituted-ammonium ions:

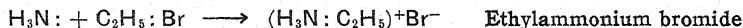


¹ This compound is frequently called *methylamine hydrochloride* and its formula written $\text{CH}_3\text{NH}_2.\text{HCl}$. The formulas of other amine salts are often written in like manner, following an early practice according to which ammonium chloride was shown as $\text{NH}_3.\text{HCl}$ instead of NH_4Cl .

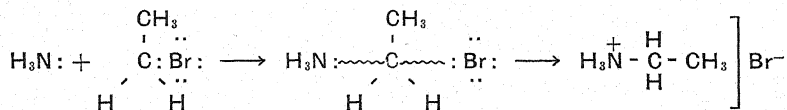
Depending upon its particular physical properties the amine thus liberated may be evolved as a gas, remain in solution, separate as an oil, or crystallize.

Laboratory Applications. Amines are frequently converted into salts in order to separate them from nonbasic organic compounds of similar physical properties. Suppose, for example, it is desired to separate an amine from a neutral compound of about the same boiling point, both being only sparingly soluble in water, freely soluble in ether, and volatile with steam. If the mixture is treated with hydrochloric acid, the amine is converted into its hydrochloride. The latter is probably soluble in water, in which case it may be dissolved away from the neutral water-insoluble impurity. Or the impurity may be separated by ether extraction or steam distillation from the ether-insoluble nonvolatile amine hydrochloride. Once separated, the salt is converted into the free amine by treating with sodium hydroxide and the amine is further purified by distillation or recrystallization.

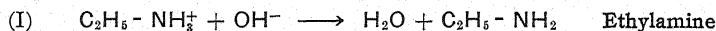
13-4 Amination and Alkylation. Ammonia and amines react with alkyl halides by addition. The reaction is analogous to salt formation except that an alkyl radical, instead of a proton, adds to the unshared electron pair of the nitrogen atom; but it occurs much less readily, as evidenced by the longer time and the higher temperatures usually required. When ammonia dissolved in ethyl alcohol is heated under pressure with ethyl bromide, the initial reaction is summarized by the equation



This and the similar reactions which follow proceed through a nucleophilic attack in which a bond between nitrogen and carbon begins to form before the bromide ion separates (cf. Sec. 7-9):



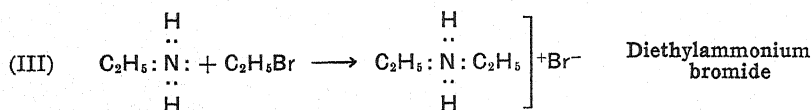
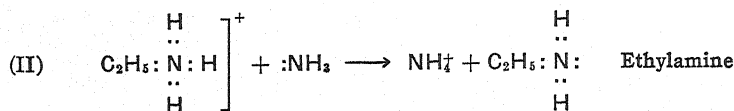
When the salt ethylammonium bromide is treated with a base, it reacts like ammonium bromide by releasing a proton; thus ethylamine is formed:



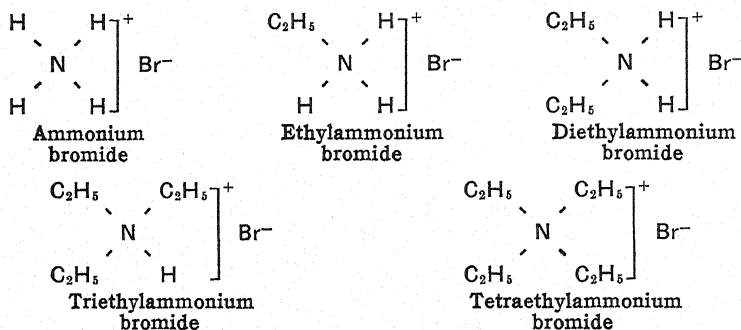
The net result is replacement of the halogen atom of ethyl bromide by the amino group. Such reactions, in which the NH_2 group is introduced into an organic molecule in place of another atom or group, are called *aminations*. This is a general reaction of halogen compounds (including, for example, halogen-substituted acids) but is usually complicated to a greater or less extent by the subsequent reactions described below.

Alkylation of Amines. When ethyl bromide and ammonia are heated together as just described, reaction does not end with the formation of

ethylammonium bromide. Excess ammonia acting on the ethylammonium ion liberates a certain amount of ethylamine, which then adds ethyl bromide:



This series of reactions continues until, in the end, there is formed a mixture of all five of the following salts:

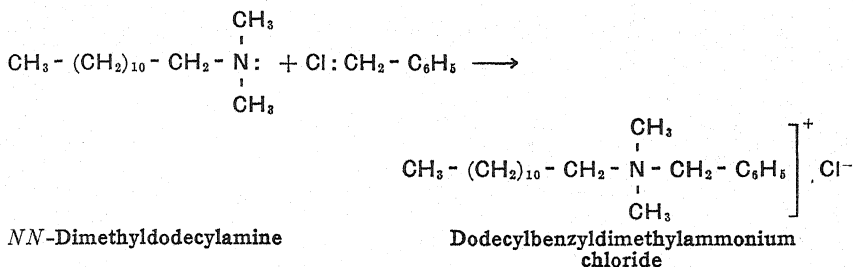


A solution of sodium hydroxide added to these salts liberates a mixture of ammonia (b.p. -33.4°C), ethylamine (b.p. 16.6°C), diethylamine (b.p. 55.5°C), and triethylamine (b.p. 89.5°C). An efficient fractionating column is required to isolate the individual compounds.

This progressive replacement of *N*-hydrogen atoms of a primary amine by alkyl radicals—*alkylation*—is the most general route to secondary and tertiary amines.

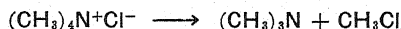
13.5 Quaternary Ammonium Compounds. The final products of alkylation, of the general type $\text{R}_4\text{N}^+\text{X}^-$, are called quaternary ammonium salts. They may be regarded as ordinary ammonium salts in which all four hydrogen atoms of the NH_4^+ ion have been replaced by hydrocarbon radicals. These compounds (*e.g.*, tetraethylammonium bromide, above) resemble simple ammonium salts in their ready solubility in water and in the high electrical conductivity of their solutions.

Special interest attaches to those quaternary ammonium salts which contain a long, normal, alkyl radical—usually C_{12} to C_{18} . These are prepared from tertiary amines by addition of an alkyl halide or an aralkyl halide such as benzyl chloride, *e.g.*,

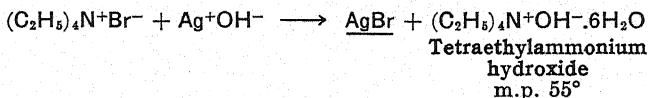


They are important surface-active agents of the cation-active type (Sec. 16-21), which have the further property of being strongly bactericidal. Uses based on this property include sterilization of the skin, of dishes, and of various appliances in the food industries.

The cation of a quaternary salt contains no hydrogen attached to the nitrogen atom. Consequently it cannot lose a proton when treated with a base like sodium hydroxide (distinction from all amine salts). When dry quaternary salts are *strongly* heated, they yield tertiary amines, *e.g.*,

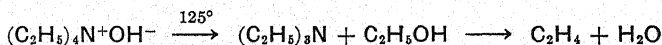


Quaternary Ammonium Bases. If a solution of tetraethylammonium bromide is shaken with silver oxide-hydroxide, silver bromide is precipitated and can be filtered off with any excess of the oxide. Evaporation of the filtrate leaves colorless hydrated crystals of tetraethylammonium hydroxide, a typical *quaternary ammonium base*:



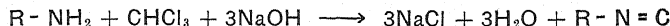
The exceptional strength of these compounds as bases places them in a class entirely apart from ammonia¹ and all amines. They furnish OH⁻ ions by direct ionization like the alkali hydroxides, K⁺OH⁻ and Na⁺OH⁻, and conductivity measurements indicate that ionization is complete. This explains why the silver oxide method is necessary in order to isolate quaternary ammonium bases from their salts.

When *heated* with sodium hydroxide, a quaternary ammonium base decomposes in the sense of the following typical equation:



¹ The fact that quaternary ammonium hydroxides, R₄N⁺OH⁻, can be isolated—usually with water of hydration, as illustrated here—is a further significant difference from ordinary “ammonium hydroxide” (Sec. 12-13).

sodium hydroxide:



These products with the structure $R.N \equiv C$ are also called *isonitriles* and *isocyanides* because they are isomeric with the corresponding nitriles. They have an offensive, penetrating odor, and the reaction is often used as a test for primary amines. The carbylamines are poisonous and should be smelled with caution.

Grignard Reaction. Primary and secondary amines react with Grignard reagents such as methylmagnesium iodide to give two or one equivalent of methane, respectively (Zerewitinoff determination, Sec. 7-17).

13-8 Sources of Alkyl Amines. Laboratory methods which give good yields of primary alkyl amines include the Hofmann reaction (Sec. 12-15), the Gabriel synthesis (Sec. 21-2), and the reduction of various types of compounds including nitriles, oximes, amides and substituted amides, and tertiary nitro compounds such as $(CH_3)_3C.NO_2$. Catalytic hydrogenation, the action of sodium or sodium amalgam in alcohol, and the action of lithium aluminum hydride are among the reducing methods used. Secondary and tertiary amines are usually made by alkylating primary amines.

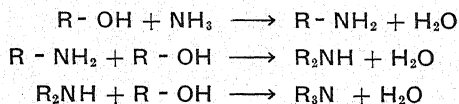
Industrial Sources. The extensive manufacture of alkyl amines began only with the Second World War, when it was stimulated by factors such as the demand for methylamine, required in producing the explosive tetryl. The increasing supply has led to the development of other industrial uses such as the manufacture of rubber-processing chemicals, dyestuffs, and synthetic detergents. Methods of production now used extensively include the following:

From the higher fatty acids. The ammonium salts of these acids are dehydrated in one operation to their nitriles, and the latter are converted into the corresponding amines by catalytic hydrogenation or by reduction with sodium and alcohol:



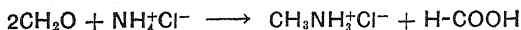
This method yields higher primary amines free from secondary.

From alcohols and ammonia. Passing a compressed and heated mixture of the vapors over a suitable catalyst always yields mixtures of amines through successive reactions of the types

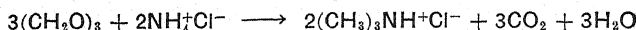


From alkyl halides and ammonia. Heating under pressure in alcoholic solution likewise yields mixtures as already described in Section 13.4. Separation of the products is especially difficult with the methyl amines, all three of which boil within the range -6.6 to 7.4°C .

A special method for obtaining methylamine and trimethylamine consists in heating ammonium chloride with anhydrous formaldehyde. By varying the conditions somewhat, this reaction may be made to proceed, mainly, in either of the two ways:



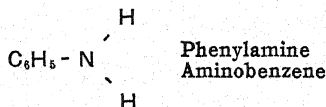
or



The amines are liberated from these salts by the action of alkali.

ARYL AMINES

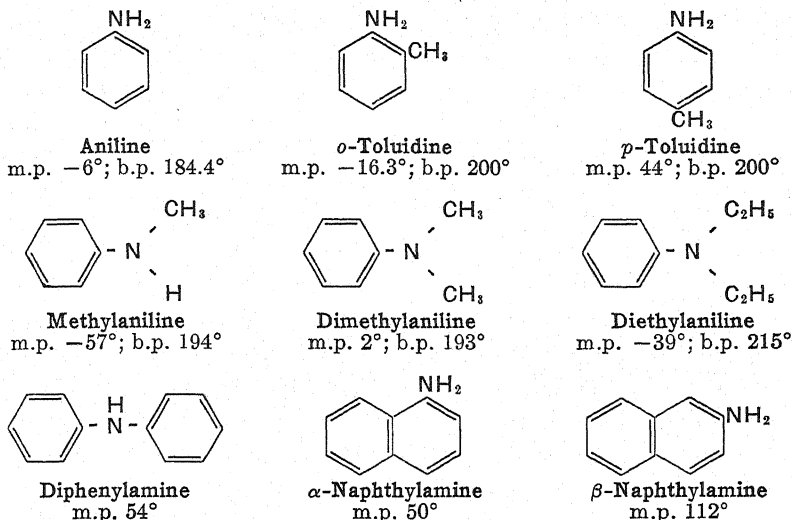
13-9 Primary aryl amines may be described either as compounds in which a hydrogen atom of ammonia has been replaced by an aryl radical or as compounds derived from an aromatic hydrocarbon by replacing a nuclear¹ hydrogen atom by an amino group. Thus, the simplest member of the family is described accurately either as phenylamine or as aminobenzene:



Actually, this compound is always called **aniline**. In the secondary and tertiary aryl amines, one or both of the remaining *N*-hydrogen atoms is replaced by a hydrocarbon radical which may be either alkyl or aryl. Examples follow.

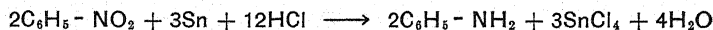
Industrial coal-tar intermediates include a number of aryl amines which are of major importance as intermediates for the manufacture of dyestuffs, rubber-processing chemicals, and other finished products (Chaps. 23 and 24). Outstanding are

¹ This definition deliberately excludes aromatic compounds like *benzylamine*, $\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$, in which the amino group is in a side chain. These compounds—which in general have little importance—rather closely resemble the alkyl amines of about the same molecular weight in all their properties, including their strength as bases. They differ sharply from the true primary *aryl* amines in that they cannot be diazotized and do not couple with diazonium ions.



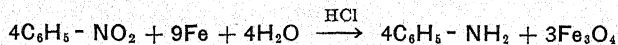
It will be noted that all these are either high-boiling liquids or solids. They dissolve freely in ether and most other organic solvents. Aniline is sparingly miscible with water; at 22°C , 100 volumes of water dissolve 3.47 volumes of aniline and 100 volumes of aniline dissolve 5.22 volumes of water. The naphthylamines and diphenylamine are practically insoluble in water. Isomerism is illustrated by the three toluidines, methylaniline, and benzylamine, all of which have the molecular formula $\text{C}_7\text{H}_9\text{N}$.

13-10 Preparation and Manufacture. The one general method for making *primary* aryl amines is reduction of the corresponding nitro compounds, many of which are readily available as nitration products of aromatic hydrocarbons. Laboratory reductions of nitro compounds to primary amines are often conducted by stirring with tin and hydrochloric acid, *e.g.*,

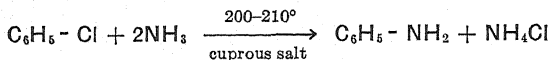


Excess acid yields the amine salt, from which the organic base is liberated by an alkali such as sodium hydroxide. (The use of milder reducing agents to obtain intermediate reduction products of nitro compounds is described in Section 23-23.) Industrially, nitro compounds are reduced to amines much more cheaply by the use of iron.¹ This is the usual

¹ In this method only enough hydrochloric acid is used to produce some ferrous chloride, which catalyzes the over-all reaction:



method for manufacturing aniline and the toluidines. Aniline is manufactured also by the amination of chlorobenzene by heating under pressure with concentrated aqueous ammonia and a copper catalyst:



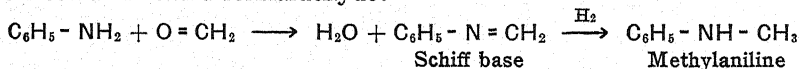
A large excess of ammonia is used in order to suppress, so far as possible, a side reaction which yields phenol:



The pressure developed at the temperature necessary for conversion to aniline is of the order of 750 to 850 psi; hence this method is restricted to industrial use in especially designed equipment (cf. Sec. 8-31).

The Bucherer reaction (Sec. 24-8) is a somewhat special method of amination, used mainly in the naphthalene series, *e.g.*, for manufacturing β -naphthylamine from β -naphthol.

Secondary and *tertiary* amines such as the methylanilines are produced by alkylating primary aryl amines. Dimethyl sulfate and diethyl sulfate are effective alkylating agents for laboratory syntheses. The usual industrial method is to heat under moderate pressure a mixture of aniline, methanol (or ethanol), and sulfuric or hydrochloric acid. When 1 mole each of aniline and methanol are thus heated with acid and the product made alkaline and steam distilled, the distillate is not pure methylaniline but always contains dimethylaniline and unchanged aniline (for the reasons explained in Sec. 13-4). In industrial practice the alkylating agent is used in excess and heating continued until substantially all aniline and methylaniline have been converted to the dimethyl compound, which is in much greater demand. Pure monomethylaniline can be made, when required, by reducing the Schiff base formed by reaction between aniline and formaldehyde:

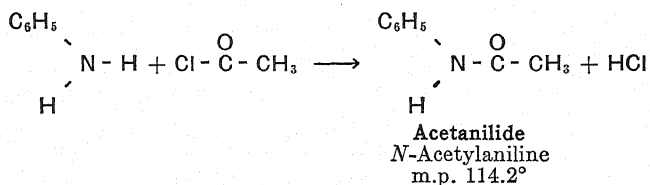


13-11 Basic Strength and Salt Formation. The aryl amines listed in Section 13-9 are, with the exception of diphenylamine, bases with ionization constants of the order of 10^{-10} . This means that their strength as bases is comparable to that of the phenols as acids and that they are much weaker bases than ammonia and the alkyl amines. They are, however, capable of forming salts with the common acids, for which reason these amines are more soluble in dilute hydrochloric acid than in water.¹

¹ The hydrochlorides of aniline and the toluidines are very soluble in water, and these amines dissolve freely in hydrochloric acid. The naphthylamine hydrochlorides are only sparingly soluble in water and are precipitated by excess of acid; but these salts are soluble enough in the 5 per cent HCl ordinarily used for classification testing to permit recognition of the parent amines as compounds having basic properties.

Diphenylamine, in which two aryl radicals are joined to the nitrogen atom, is so feebly basic ($K_b = \text{ca. } 1 \times 10^{-13}$) that it dissolves only in concentrated sulfuric acid and is precipitated when this solution is diluted with water. Triphenylamine, $(\text{C}_6\text{H}_5)_3\text{N}$, shows no basic properties whatsoever. Basicity is also reduced by electronegative groups (*e.g.*, NO_2) attached to an aryl radical and virtually disappears when any *acyl* radical is attached to the nitrogen atom as in acetanilide. In summary, *all electron-attracting atoms and groups reduce the strength of amines as bases*. They render the unshared electron pair on the nitrogen atom less available for proton binding, as explained more fully in Section 22·12.

13·12 Acylation of Amines. Acid chlorides react with primary and secondary amines to give products in which one *N*-hydrogen atom is replaced by an acyl radical, *e.g.*,



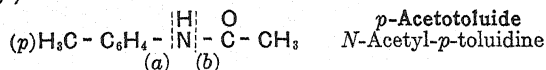
Acetic anhydride and aniline yield this same product. Primary and secondary amines are frequently converted also into their *N*-benzoyl derivatives by shaking with benzoyl chloride and sodium hydroxide (*cf.* Schotten-Baumann reaction, Sec. 12·10). Tertiary amines cannot be acylated since they do not contain an *N*-hydrogen atom.

The *N*-acyl amines are usually crystalline solids with definite melting points and low solubility in water. They are often prepared as derivatives for the identification of amines and of carboxylic acids (Sec. 12·19). Those which structurally are *N*-acyl derivatives of aniline are called *anilides*, and those related in like manner to the toluidines (*o*, *m*, or *p*) are *toluides*.

Acylation of an amine produces the following significant changes in chemical properties: (1) The reactivity of any remaining *N*-hydrogen atom is much reduced, *e.g.*, acetanilide shows little tendency toward further acylation. (2) The basic property of the parent amine is obliterated, and the *N*-acyl amines are substantially neutral. (3) Activation of the *ortho* and *para* positions is reduced; this makes it possible, for example, to prepare *p*-bromoacetanilide under conditions which with aniline would result in tribromination. (4) The molecule is protected against oxidation (Sec. 13·15).

It will be noted that any acylated amine contains two carbon-nitrogen

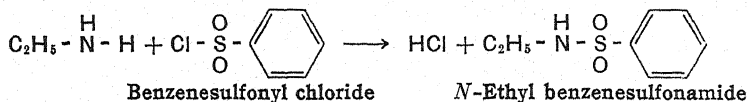
linkages, *e.g.*,



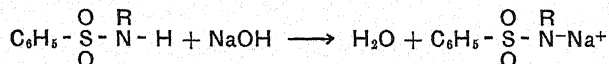
One of these (a) is typical of the amines, while (b) is that of an amide. Consequently (b) is readily split by hydrolysis, either with acid or alkali catalysts, while (a) is unaffected. Thus *p*-acetotoluide yields, by acid hydrolysis, acetic acid and *p*-toluidine hydrochloride and, by alkaline hydrolysis, *p*-toluidine and an acetate.

Acetanilide is the most important compound of its class. It is manufactured on a very large scale by heating under reflux a mixture of aniline and glacial acetic acid.¹ Acetanilide is used medicinally to reduce fever (antipyretic) and to lower sensitivity to pain (analgesic). Its major use is as an intermediate in the manufacture of other chemical products, notably the sulfa drugs.

13-13 Hinsberg Reaction. Primary and secondary amines also react with sulfonyl chlorides and yield substituted sulfonamides (Sec. 14-5), *e.g.*,



The reaction is effected by shaking the amine with benzenesulfonyl chloride and an excess of a solution of sodium hydroxide (cf. Schotten-Baumann reaction, Sec. 12-10). The sulfonamides formed from *primary* amines dissolve in the alkali present through reactions of the type



Those derived from secondary amines have no hydrogen on the N atom and are insoluble in alkali. Tertiary amines do not react with sulfonyl chlorides.

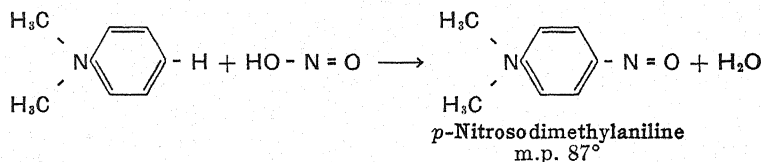
The application of these differences to distinguishing between the three classes of amines (and, frequently, to separating mixtures of them) is called the Hinsberg reaction. Details may be found in laboratory manuals.

13-14 Nuclear Reactions. The NH₂ group (and also NHR and NR₂, if R is an alkyl radical) is strongly *ortho*- and *para*-directing and highly activates these positions. For example when a dilute water solution of aniline is treated with bromine water, three hydrogen atoms are quickly substituted and 2,4,6-tribromoaniline precipitates. The special

¹ The initial reaction is formation of the salt phenylammonium acetate which, on heating, loses a molecule of water to form acetanilide. (Under similar conditions ammonium acetate gives acetamide.) This is the cheapest way to make acetanilide and illustrates a third general method for acylating an amine.

reactivity of the *para* hydrogen atom is shown also in its ability to enter into various substitution reactions which either do not occur at all with the parent hydrocarbons or else are too slow for practical results. These include nitrosation, described below, and various others (arsonation, coupling, etc.) to be considered later. This activating effect of the NH_2 group in aryl amines—which is even more powerful than that of the OH group in phenols—arises through resonance with the nucleus (Sec. 22·12).

Nitrosation. Nitrous acid reacts by substitution with the *para* hydrogen atom of a *tertiary aryl* amine such as dimethylaniline:



This substitution reaction by nitrous acid is called *nitrosation*, by analogy to nitration, sulfonation, etc. It does not occur with benzene and most other aromatic compounds but is observed only at the highly activated *para* position of tertiary aryl amines and phenols.

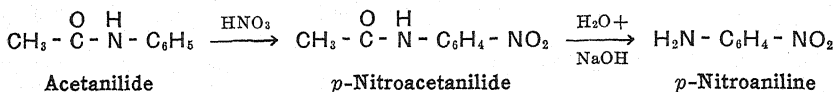
Secondary aryl amines react with nitrous acid like the same type of alkyl compounds to give *N*-nitrosoamines. *Primary* aryl amines are diazotized by nitrous acid as described below (Sec. 13·16).

Hydrogenation. Aniline is hydrogenated by nickel catalysis rather more easily than benzene. It adds six hydrogen atoms to the nucleus, forming cyclohexylamine, $\text{C}_6\text{H}_{11}\text{NH}_2$. The latter resembles the alkyl amines of about the same molecular weight in all essential properties; it is a much stronger base than aniline, the *ortho* and *para* positions show no special reactivity, it cannot be diazotized, and it does not couple with diazonium salts.

13·15 Oxidation; Protection. Primary and secondary aryl amines are very sensitive to oxidation, even by atmospheric oxygen. The formation of relatively small amounts of oxidation products of unknown structure explains the fact that, although colorless when freshly prepared and purified, they gradually develop dark colors. It is sometimes possible to prepare specific oxidation products by the suitable choice of chemical oxidizing agents and the control of conditions; *e.g.*, cold dichromic acid converts aniline into benzoquinone (Sec. 23·20), and the same reagent, hot, oxidizes it to the dyestuff called Aniline black. By and large however, the important fact to remember is that the NH_2 and NHR groups render the ring sensitive to oxidation and that, therefore, *primary and secondary amines cannot be nitrated directly or exposed to the conditions*

necessary for oxidizing a side chain. Such treatments always lead to rupture of the ring and yield little except tarry mixtures.

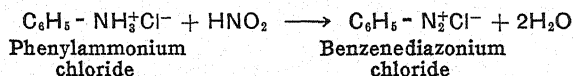
Ring cleavage can be avoided by *protecting* a NH_2 or NHR group by acylation. For example, *p*-nitroaniline is obtainable from aniline in good yield as follows: aniline is converted into acetanilide; this can be mononitrated smoothly at around 0°C ; finally, the protecting acetyl group is removed by hydrolysis:



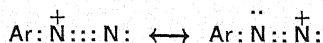
In like manner, *o*-toluidine can be oxidized successfully to *o*-aminobenzoic acid by proceeding through *o*-acetotoluide.¹

13.16 Diazo Compounds. Primary aryl amines react with nitrous acid to form diazonium salts. This reaction, which is called *diazotization*, and the further reactions of its products are among the most useful in the whole field of synthetic organic chemistry.

The usual procedure for diazotization is to dissolve one mole of amine in about three moles of concentrated hydrochloric acid, chill in an ice bath to 0 to 5°C , and slowly stir in a solution containing one mole of sodium nitrite. The excess hydrochloric acid liberates the required nitrous acid from the nitrite. The over-all reaction (details of which are still not clear) is the conversion of the substituted ammonium ion into a *diazonium* ion, *e.g.*,



The water-soluble diazonium salts thus formed are seldom isolated, for they are unstable and often explosive when dry, but ordinarily¹ are used promptly in the cold solutions in which they are formed. They are strong electrolytes, thus indicating an ionic bond between Cl^- (or other anion) and the electron-deficient diazonium ion. The latter is a hybrid cation with a structure intermediate between the extreme forms



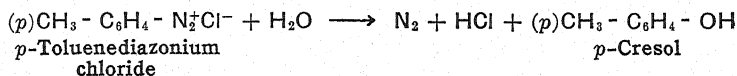
The noncommittal formula $\text{Ar}.\text{N}_2^+$ suffices for many purposes.

The synthetic uses of diazonium salts include many reactions in which an atom or group displaces N_2 from the molecule, some of which are described below, and the important reaction of *coupling* (Sec. 25.9) which is widely used in the manufacture of dyestuffs.

¹ See Section 25.21 with regard to "stabilized" diazonium compounds now used extensively in one method of dyeing.

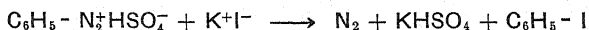
13-17 Diazo Reaction; Nitrogen Replacements. In all the following reactions the two nitrogen atoms of a diazonium salt leave the ion as gaseous nitrogen and are replaced by a negative ion or group. The exact mechanism is still uncertain and probably varies in different replacements; hence no attempt is made to indicate more than the over-all changes.

Introduction of Hydroxyl. When the water solution of a diazonium salt is allowed to become warm, or is intentionally heated, nitrogen is evolved and OH enters the molecule to form a phenol, *e.g.*,



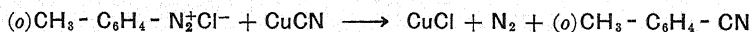
This is a major laboratory method for making phenols. The tendency toward this reaction explains the need for preparing and preserving diazonium salts at low temperatures and, also, why other compounds prepared by the diazo reaction contain phenolic by-products.

Introduction of Halogen. Any one of the four halogens can be brought into combination with the aromatic nucleus through a diazonium salt. For iodine, it suffices to add a solution of potassium iodide and warm, *e.g.*,



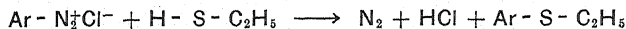
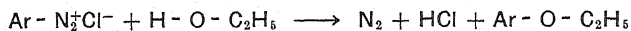
(Sulfuric rather than hydrochloric acid is used in preparing diazonium salts for halogen replacements in order to avoid the presence of competing chloride ions.) Bromine and chlorine are introduced in like manner in the presence of finely divided metallic copper (*Gattermann* reaction) or by reaction between the diazonium salt and freshly prepared cuprous chloride or cuprous bromide (*Sandmeyer*). The diazo reaction is the most satisfactory of all methods for introducing iodine into aromatic compounds. It is useful also for introducing chlorine and bromine when, for any reason, direct substitution is undesirable. Fluorine can be introduced by heating an aryl diazonium fluoride, or by treating a diazonium chloride with a mixture of hydrofluoric and boric acids.

Introduction of CN. A diazonium salt can be converted into the next higher nitrile by warming its *neutralized* aqueous solution with cuprous cyanide, *e.g.*,

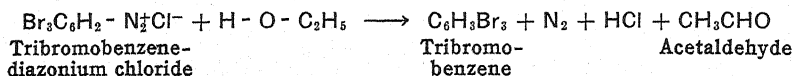


Since the resulting nitriles are readily hydrolyzed to carboxylic acids, this use of the diazo reaction amounts to a general method for attaching the COOH group to an aryl nucleus.

Other Substitutions. When a diazonium salt is isolated and heated with an alcohol or a thioalcohol, an ether or a thioether is usually obtained, *e.g.*,

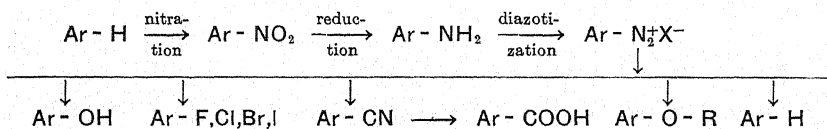


But with halogen atoms or nitro groups attached to the aryl nucleus, the prevailing reaction is the replacement of N_2 by *hydrogen*, *e.g.*,



Arsenic, also, can be brought into combination with the aryl nucleus by the aid of the diazonium salts (Bart reaction, Sec. 14.14).

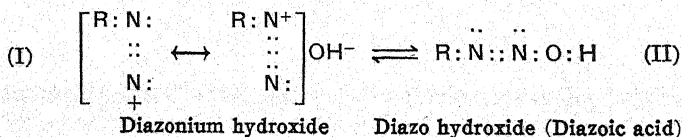
13.18 The wide use of the diazo reaction in synthetic organic chemistry depends upon the following facts: (1) Many nitro compounds can be readily obtained by nitrating hydrocarbons and other aromatic compounds. (2) Each of these can be reduced to a compound containing the NH_2 group directly attached to nuclear carbon. (3) Any compound containing this group can be diazotized. (4) Each of the resulting diazonium salts can enter into the various reactions just described. These relations are summarized as follows:



The only important limitation on the general use of this method arises from directing influences which sometimes prevent the introduction of the original NO_2 group in the position desired.

13.19 Diazotates. Diazonium salts are, as has been indicated, well ionized in solution. From such solutions, silver hydroxide precipitates diazonium hydroxides. These are unstable and decompose rapidly but, when tested immediately after they are formed, have been shown to be bases considerably stronger than ammonia. This argues for an *ionic* bond (I) between the hydroxide and diazonium ions as in quaternary ammonium bases.

When a solution of a diazonium salt is poured into excess of cold concentrated potassium hydroxide solution, it yields a potassium compound called a *diazotate*.



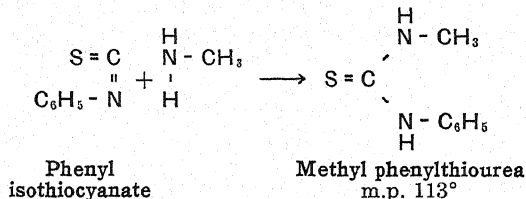
This is the salt of a weak acid, known as a *diazoic acid* or *diazo hydroxide*, which appears to have the structure shown in (II). Related compounds are known in which, for example, CN replaces OH. The diazotates exist in isomeric forms which are regarded as geometrical isomers (Sec. 15-24), in which the double bond prevents rotation:



13-20 Detection and Identification of Amines. All organic compounds containing nitrogen and having *basic* properties are either amines or closely related substances. Compounds insoluble in water are recognized as having basic properties if they dissolve in dilute hydrochloric acid; water-soluble bases give alkaline solutions requiring an appreciable quantity of acid for neutralization. Amines that are extremely weak bases appear among the neutral nitrogen compounds in any scheme of classification by solubilities. Aside from the different types of amines described in this chapter and a few hydrazines, the commonest organic bases are the alkaloids and other heterocyclic compounds of nitrogen, such as pyridine and quinoline (Chap. 26).

Primary amines give the carbylamine test and react vigorously with acetyl chloride; *secondary* amines react with acetyl chloride but do not give the carbylamine test; *tertiary* amines do not respond to either of these tests. A further distinguishing method is the Hinsberg reaction. A useful test for primary *aryl* amines depends on the production of intensely colored dyes by the reactions of diazotization and coupling (Sec. 25-9).

Derivatives for the final identification of primary and secondary amines are usually prepared by reactions with acetyl chloride, benzoyl chloride, or benzenesulfonyl chloride (or with related compounds such as *p*-toluenesulfonyl chloride and *m*-nitrobenzenesulfonyl chloride). Phenylthioureas are also useful derivatives, obtained by reaction between an amine and phenyl isothiocyanate, *e.g.*,



The most useful derivatives for tertiary amines are salts of acids such as picric and chloroplatinic (H_2PtCl_6) and addition products with methyl iodide and with methyl *p*-toluenesulfonate.

Questions

1. (a) Define amines in terms of their structural relationship to ammonia. (b) Do the same for amides. (c) How do compounds of these two classes differ from each other with respect to the ability to act as bases and to their behavior on boiling with dilute sodium hydroxide solution?
2. Write the structural formulas of two amines of the composition $\text{C}_4\text{H}_{11}\text{N}$ other than those given in Section 13-1, and name them.
3. Outline a practical method for separating a mixture of equal parts of an amine and an alcohol, assuming that both are insoluble in water and have nearly the same boiling point.

4. Write the structural formulas of the salts of *n*-butylamine with the following acids: hydrobromic, acetic, sulfuric, picric (Sec. 23-10).

5. Write structural equations for the reactions, if any, to be expected under the following conditions and describe any physical evidences of reaction which could be readily observed: (a) ethylamine is dissolved in water; (b) diethylamine is dissolved in hydrochloric acid and sodium nitrite is added; (c) *n*-butyl amine is treated similarly with nitrous acid; (d) isopropylamine is heated with chloroform and an alkali; (e) trimethylammonium chloride is treated with a solution of sodium hydroxide; (f) solid tetraethylammonium chloride is strongly heated.

6. Starting with propionic acid, write equations for all steps necessary in preparing: (a) *n*-propylamine; (b) ethylamine.

7. Describe and illustrate the most general method for the manufacture of primary aryl amines from the corresponding hydrocarbons.

8. Show in detail why the reaction between aniline, methanol, and sulfuric acid yields a *mixture* of amines.

9. (a) Write structural equations for the reactions involved in the manufacture of acetanilide. (b) Give equations illustrating two other methods for acylating amines. (c) In what ways does acylation alter the physical and chemical properties of aniline?

10. (a) Name acetanilide accurately as a derivative of aniline and as a derivative of acetamide. (b) Show how these relations of acetanilide enable us to predict which of its two carbon-nitrogen linkages will be split by hydrolysis.

11. (a) Write the structural formulas of *N*-propionylaniline and of *N*-benzoyl-ethylamine. (b) Rename these compounds as *substituted amides*.

12. It is desired to prepare anthranilic acid (*o*-aminobenzoic acid) from *o*-toluidine by oxidizing the methyl side chain with permanganate. Write equations for the reactions involved, including the necessary protection of the amino group. (The oxidation is conducted in a nonacidic solution, where the inorganic reduction product is hydrated MnO_2 .)

13. (a) Define "diazotization" and describe how it is conducted. (b) To what class of amines is the reaction limited? (c) How does benzylamine differ from *p*-toluidine in its behavior toward cold nitrous acid?

14. Write structural equations for the reactions to be expected when the following compounds, dissolved in hydrochloric acid and mixed with crushed ice, are treated with a solution of sodium nitrite: (a) *o*-toluidine; (b) 2-naphthylamine; (c) *p*-nitroaniline.

15. Show how the following compounds can be prepared through the diazo reaction: (a) *p*-iodotoluene from *p*-nitrotoluene; (b) *m*-nitrophenol from *m*-nitroaniline; (c) *p*-chlorobenzoic acid from *p*-nitrochlorobenzene; (d) *o*-toluic acid, $\text{CH}_3\text{C}_6\text{H}_4\text{COOH}$, from toluene.

16. (a) Explain the origin of the phenolic impurities nearly always present in aryl halides and nitriles prepared through the diazo reaction. (b) Suggest a simple chemical treatment by which these impurities can be removed.

17. Explain fully why the diazo reaction can be used for the preparation of such a large number of derivatives of the aromatic hydrocarbons.

18. (a) If an organic compound is insoluble in water but dissolves readily in dilute hydrochloric acid, what element besides carbon and hydrogen is almost certainly present? Why? (b) Are there any amines that do not act as bases? (c) An unknown substance is mixed with soda lime and heated. If it gives off a gas that smells like ammonia and turns moist litmus paper blue, how can you readily determine whether the gas is ammonia or an alkyl amine? (d) An organic compound has been shown to contain both chlorine and nitrogen. It dissolves readily in cold water, giving

a solution that is either neutral or faintly acidic. What is the probable nature of the compound? (e) An organic compound contains nitrogen. If it dissolves in water and if sodium hydroxide causes the separation of an insoluble oil, what is the probable nature of the substance?

19. An organic compound containing nitrogen is insoluble in water but dissolves in dilute acids. What conclusion would you reach regarding its type if *one* of the following additional observations were made? (a) The substance is shaken with benzoyl chloride and a solution of sodium hydroxide; at the end of the reaction, the mixture is shaken with ether and the substance extracted has the same boiling point as the original compound. (b) The substance gives an intensely disagreeable odor when boiled with alkali and chloroform. (c) The substance is shaken with benzenesulfonyl chloride and alkali; the reaction mixture is shaken with ether, and the latter extracts a solid of higher melting point than the original compound.

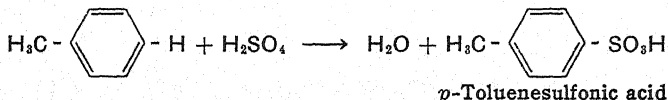
CHAPTER 14

SULFUR AND ORGANOMETALLIC COMPOUNDS

Previous chapters have dealt with the hydrocarbons and with some simple derivatives containing halogen, oxygen, and nitrogen atoms, either separately or together. A few organic compounds containing sulfur have likewise been mentioned. The present chapter surveys the more important types of organic sulfur compounds, together with a few in which carbon is joined to various other elements.

ORGANIC SULFUR COMPOUNDS

14.1 Arylsulfonic Acids. The replacement of a nuclear hydrogen atom by the SO_3H group through the action of sulfuric acid has been described already (Sec. 5.11) as one of the characteristic reactions of *aromatic* compounds. The products are sulfonic acids, $\text{Ar}.\text{SO}_3\text{H}$, in which sulfur is linked directly to carbon, *e.g.*,



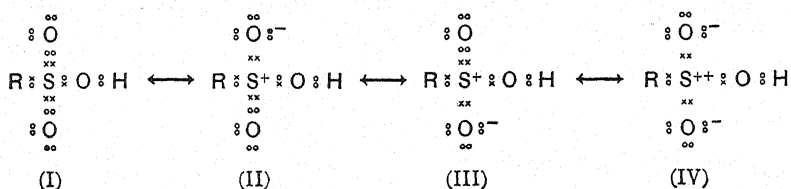
With suitable variations in concentration of the acid,¹ the proportions of reactants, and the temperature, most aromatic compounds can be converted into mono- or polysulfonic acids. The fact that the SO_3H group is *meta*-directing and deactivating toward further nuclear substitutions has also been mentioned.

The physical properties of the sulfonic acids indicate that they are highly polar substances. Unlike carboxylic acids they are strong electrolytes, comparable to HCl and H_2SO_4 ; consequently, they are not displaced from their salts by these inorganic acids. They are nonvolatile, crystalline solids that are practically insoluble in nonpolar solvents but

¹ Industrial "concentrated" sulfuric acid usually contains about 93 per cent by weight of H_2SO_4 , the remainder being water; this is commonly called *oil of vitriol*. *Fuming* sulfuric acid, generally known as *oleum*, is anhydrous H_2SO_4 in which a certain amount of SO_3 is dissolved; the usual grades contain 20, 25, or 65 per cent of excess SO_3 . By mixing oil of vitriol and oleum, 100 per cent sulfuric acid can be made; or, by using a larger proportion of oleum, it is possible to prepare sulfonating agents of *effective* concentrations corresponding to 105, 110, or some other desired percentage of H_2SO_4 .

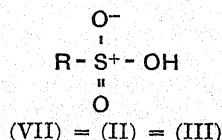
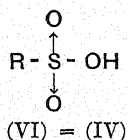
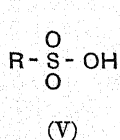
generally dissolve freely in water. Many of them crystallize with water of hydration. This strong affinity for water is often utilized to give water solubility to dyes, drugs, and other compounds by introducing SO_3H groups. The products may be used as such or, more commonly, in the form of their sodium salts (sulfonates).

14-2 The sulfur atom in a sulfonic acid carries a high $+\delta$ charge, and a corresponding negative charge is spread over the oxygen atoms. This polarity arises in part by induction, as may be seen by comparing the value for sulfur, 2.5, with the oxygen value, 3.5, in the electronegativity scale (Sec. 1.9). The $+\delta$ charge on sulfur is much increased by a high degree of resonance between extreme forms such as



(where the valence electrons of sulfur are represented by the symbol \times). In (II) and in (III) the sulfur atom is regarded as forming a coordinate covalence, in turn, with each of two oxygen atoms;¹ (IV) indicates two such bonds. The over-all effect is a high electropositive charge on the sulfur atom, which has important consequences: (1) The SO_3H group is highly polar and thus promotes solubility in water. (2) Release of its hydrogen atom as hydronium ion is facilitated, with the result that sulfonic acids are highly ionized. (3) When the SO_3H group is attached to an aryl nucleus, the $+\delta$ sulfur atom tends to withdraw electrons from the ring—thus explaining the *meta*-directing and deactivating effect (Sec. 22-8).

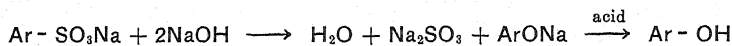
It suffices for many purposes to represent a sulfonic acid simply as $\text{R}.\text{SO}_3\text{H}$ or $\text{R}.\text{SO}_2\text{OH}$; or (V) may be used to indicate more clearly the relative positions of the atoms. When the $+\delta$ charge on sulfur needs emphasis, formulas such as (VI) and (VII) are used by different authors.



¹ Compare the polarization of the $\text{S}=\text{O}$ bond indicated here with that of the $\text{C}=\text{O}$ bond in aldehydes and ketones (Sec. 10-4).

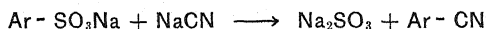
14-3 Chemical Properties. The direct sulfur-carbon linkage in the sulfonic acids and their derivatives is extremely stable. The only important reactions in which it is broken are the following:

1. *Replacement of SO₃H by OH*, by fusion of a sodium sulfonate with sodium hydroxide, has been described already (Sec. 8-31) as one of the major methods for the manufacture of phenols:



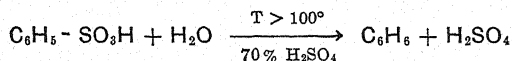
While not so important as formerly for the synthesis of C₆H₅OH, it is still used for that purpose and for the manufacture of β-naphthol and other intermediates derived from naphthalene.

2. *Replacement of SO₃H by CN* can be effected by strongly heating a dry mixture of an aryl sulfonate with sodium cyanide:



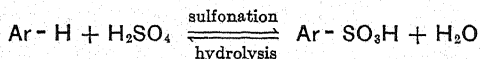
Since the CN group is readily hydrolyzed to carboxyl, this amounts to a method for replacing SO₃H by COOH. The yields, however, are poor, and the reaction is much less important than the phenol synthesis.

3. *Replacement of SO₃H by H*. The sulfur-carbon bond in the sulfonic acid is not split by boiling with water or with dilute solutions of acids or bases (in contrast with the C—O—S bond in the esters of sulfuric acid). But an arylsulfonic acid can be hydrolyzed by superheated steam in the presence of strong sulfuric acid, *e.g.*,



The principal application of the reaction is the removal of SO₃H groups which have been introduced for some temporary purpose or which may have entered undesired positions.

The occurrence of this last reaction implies that (unlike nitration and chlorination) the sulfonation of aromatic compounds is reversible:



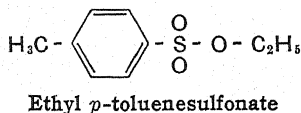
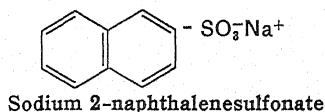
This explains why temperature often has a great influence on the position entered by the SO₃H group. A conspicuous example is the monosulfonation of naphthalene. Up to 80°C, over 96 per cent of the product is the 1-sulfonic acid; but if the reaction mixture is raised to 165°C for a time, it is possible to obtain an 85 per cent yield of 2-naphthalenesulfonic acid. Thus it appears that the 1-acid is the more easily formed; but at higher temperatures it is more rapidly hydrolyzed to sulfuric acid and naphthalene—which is resulfonated in the 2 position.

2-Naphthalenesulfonic acid is the product usually wanted (in order to make β-naphthol). To purify it from the 15 per cent of the 1-isomer present in the product

obtained at 165°C, advantage is taken of the relative rates of hydrolysis. Live steam is blown into the sulfonated mixture, which is still strongly acid. The 1-sulfonic acid is hydrolyzed rapidly, and the resulting naphthalene distills out with the steam.

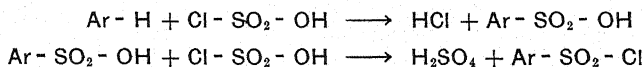
14.4 Derivatives of Sulfonic Acids. Either H or OH of the SO_3H group can be replaced, by reactions similar to those of the COOH group, to yield corresponding types of acid derivatives—salts, esters, acid chlorides, and amides.

Sulfonates. Both the salts and esters of sulfonic acids are called sulfonates, *e.g.*,

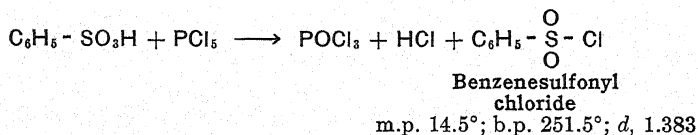


The esters are of minor importance in comparison with those of carboxylic acids. *Sodium* sulfonates are the commonest salts. They are readily formed by neutralizing sulfonic acids with sodium hydroxide or sodium carbonate and are quite soluble in water. Their use in the manufacture of phenols by alkali fusion was mentioned above. Also the many dyes, synthetic detergents, etc., into which SO_3H groups have been introduced to give water solubility, are generally used in the form of sodium salts. Calcium and barium sulfonates, which are much less soluble in water, are sometimes prepared as intermediates in the isolation of sulfonic acids.

Sulfonyl chlorides can be obtained directly from aromatic hydrocarbons by heating with an excess (more than two equivalents) of chlorosulfonic acid. The reaction probably occurs in stages as follows:

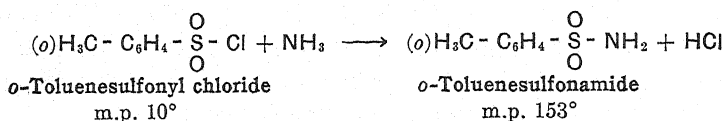


They are usually prepared in the laboratory by heating a sulfonic acid or a sodium sulfonate with phosphorus pentachloride, *e.g.*,



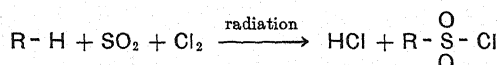
Other arylsulfonyl chlorides resemble benzoyl chloride in the method of preparation just described, in their structure, and in their chemical properties. They are hydrolyzed only slowly by cold water and alkalies but, on boiling, reaction goes to completion. Their most important reaction is the formation of sulfonamides.

14.5 Sulfonamides. Sulfonyl chlorides react like benzoyl chloride with ammonia, yielding sulfonamides, *e.g.*,



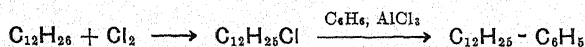
They react in like manner with primary and secondary amines such as aniline, *p*-toluidine, and methyl aniline to give arylsulfonamides, etc. (cf. Hinsberg reaction, Sec. 13.13). These and the sulfonamides are usually crystalline compounds of sharp melting points and are only slightly soluble in water. They are the derivatives most commonly prepared for the identification of sulfonic acids, sulfonates, and sulfonyl chlorides. The "sulfa" drugs (Sec. 23.26) are closely related to benzenesulfonamide.

14.6 Alkylsulfonic Acids. Most paraffin hydrocarbons do not react with sulfuric acid except at high temperatures, and then sulfonation is accompanied by much oxidation. For this reason alkylsulfonic acids were of little importance until recently. The situation was changed by the development of the Reed method for making their sulfonyl chlorides by reaction with sulfur dioxide and chlorine in the presence of visible light of the shorter wave lengths:



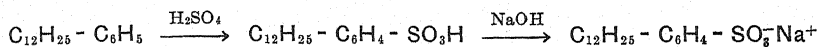
The chlorides are readily hydrolyzed and converted into sodium sulfonates, $\text{R}.\text{SO}_3^-\text{Na}^+$. When this procedure is applied to a mixture of C_{11} to C_{18} alkanes, obtained from the kerosene and white-oil distillates from paraffin-base petroleum, it yields an important type of synthetic detergent (Sec. 16.21).

Alkyl-arylsulfonates. These compounds, which are produced in larger amounts than any other synthetic detergents (Nacconol, Santomerse, etc.) are likewise made from an alkane kerosene¹ distillate. This is chlorinated and the product, often called *keryl* chloride, condensed with benzene by the Friedel-Crafts reaction, *e.g.*,



The benzene nucleus can then be sulfonated readily as in other aromatic compounds and the resulting mixture of sulfonic acids converted into sodium salts:

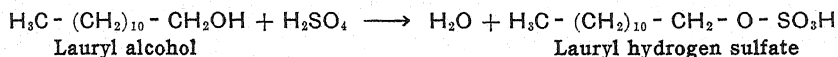
¹ Alternatively, propene is polymerized to a mixture consisting mainly of $\text{C}_{12}\text{H}_{24}$, which is used to alkylate benzene.



Since hydrocarbons are the raw materials, both these types of sulfonate detergents can be produced more cheaply than the sulfates described in the next section.

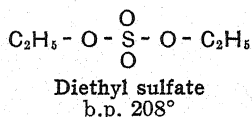
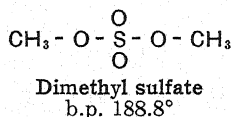
14.7 Esters of Sulfuric Acid. The lower monoalkyl esters, or alkyl hydrogen sulfates, were considered in Section 8.11 in relation to their formation from alcohols. There it was noted also that the ester linkage, C—O—S, is split by hydrolysis much more readily than the direct C—S bond of the sulfonic acids and sulfonic acid derivatives.

The higher monoalkyl sulfates constitute a third important type of synthetic detergent. Mixtures of the necessary long-chain alcohols, from about C₁₂ to C₁₈, are obtained by reduction from the natural fats and fatty oils (Sec. 16.22) and are esterified with sulfuric acid, *e.g.*,

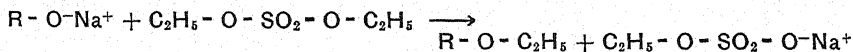


The mixed sodium salts (Gardinol detergents) are marketed under trade names such as Dreft and Drene. Their salts with triethanolamine are widely used in shampoos.

Dialkyl Sulfates. The best known and most useful of the dialkyl sulfates, or normal esters of sulfuric acid, are

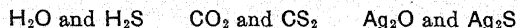


Both these compounds are useful alkylating agents for alcohols, phenols, and amines. Their higher boiling points give them advantages for this purpose over the methyl and ethyl halides. A typical alkylation is represented by the equation



At higher temperatures both alkyl groups can be utilized.

14.8 Compounds Containing Reduced Sulfur. Sulfur appears in the periodic table in the same group with, and just below, oxygen. Both have six valence electrons. When the sulfur atom is in its lowest state of oxidation, as in hydrogen sulfide and the metallic sulfides, it acts in many ways like oxygen and both elements form analogous compounds, *e.g.*,



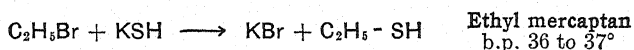
Included are many organic compounds similar to alcohols, ethers, etc. These are commonly called *thio* compounds and are said to contain

reduced sulfur. Examples include:

Oxygen Series	Sulfur Series
$\text{C}_2\text{H}_5:\ddot{\text{O}}:\text{H}$	$\text{C}_2\text{H}_5:\ddot{\text{S}}:\text{H}$ Ethyl mercaptan; ethanethiol
$\text{C}_6\text{H}_5:\ddot{\text{O}}:\text{H}$	$\text{C}_6\text{H}_5:\ddot{\text{S}}:\text{H}$ Thiophenol; phenyl mercaptan
$\text{C}_2\text{H}_5:\ddot{\text{O}}:\text{C}_2\text{H}_5$	$\text{C}_2\text{H}_5:\ddot{\text{S}}:\text{C}_2\text{H}_5$ Ethyl thioether; diethyl sulfide
$\text{H}_3\text{C}-\overset{\text{O}}{\underset{\cdot\cdot}{\text{C}}}:\ddot{\text{O}}:\text{H}$	$\text{H}_3\text{C}-\overset{\text{O}}{\underset{\cdot\cdot}{\text{C}}}:\ddot{\text{S}}:\text{H}$ Thioacetic acid

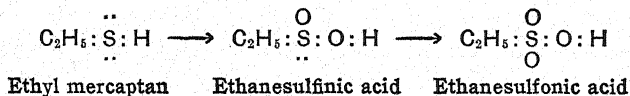
In general, our knowledge of thio compounds is less complete than that of their oxygen analogues. Useful applications are also much rarer. Nonetheless, reduced sulfur appears in several substances of the greatest biochemical importance, including vitamin B₁ (thiamine) and two of the amino acids, cystine and methionine, which occur in the proteins (Table 21.1). Reduced sulfur atoms are found in the rings of various heterocyclic compounds including thiophene and the drug sulfathiazole.

14.9 Mercaptans; Thioethers. Mercaptans (*thiols*) can be made by heating an alkyl halide or an alkyl sulfate with a concentrated solution of potassium hydrogen sulfide, *e.g.*,



They are compounds of intense and disagreeable odor, recognizable in minute traces; thus the addition of amyl mercaptan, $\text{C}_5\text{H}_{11}\text{SH}$, to odorless illuminating gas makes possible the ready detection of leaks. The use of small amounts of dodecyl mercaptan in the manufacture of GR-S synthetic rubber has been mentioned (page 106, footnote 2).

The most marked difference in chemical behavior of the mercaptans as compared with the alcohols arises from the fact that the sulfur atom itself can be oxidized by suitable reagents, *e.g.*,

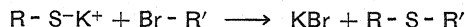


Aliphatic sulfonic acids were made in laboratory quantities by the oxidation of mercaptans long before they could be obtained from the hydrocarbons (Sec. 14.6).

The term mercaptan (from *mercurium captans*, seizing mercury) came from the early observation that these compounds react avidly with mercuric oxide to form stable insoluble salts such as $(\text{C}_2\text{H}_5\text{S})_2\text{Hg}$. The latter are called mercaptides. Lead mercaptides are among the products formed when an alkaline suspension of lead oxide

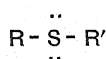
is used to remove sulfur compounds from gasoline. This refining step is important because the presence of reduced sulfur decreases the susceptibility of gasoline to improvement by tetraethyllead.

Thioethers can be prepared by heating alkyl halides with potassium sulfide, K_2S , or by a method analogous to the Williamson synthesis of the ordinary ethers, *e.g.*,

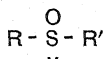


It will suffice to describe the two chemical properties which are unusual:

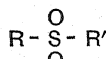
The sulfur atom in a thioether can be oxidized as in a mercaptan, yielding first a sulfoxide and then a sulfone:



Thioether

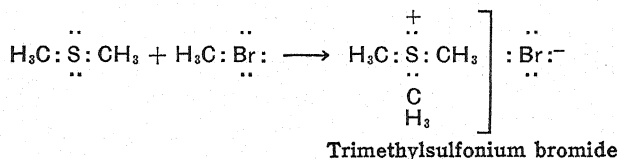


Sulfoxide

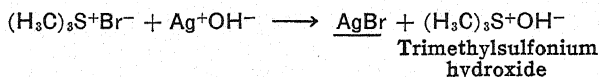


Sulfone

Thioethers readily add alkyl halides to give sulfonium salts, *e.g.*,

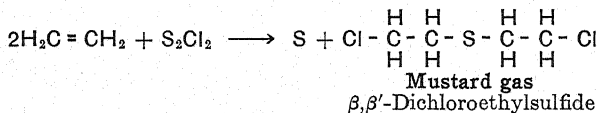


These salts are highly ionized and otherwise resemble quaternary ammonium salts. When treated with moist silver oxide, they yield sulfonium hydroxides which are strong bases:



It will be recalled that ordinary ethers form somewhat similar but much less stable *oxonium* compounds.

Mustard gas, an effective chemical-warfare agent, is a thioether made from ethylene by reaction with sulfur chloride:



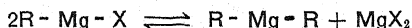
Mustard "gas" is not a gas, but a liquid of high boiling point (120°C at 34 mm). It is effective in shells which, when they burst, spray it widely. On contact with the skin or mucous membranes it somewhat slowly produces an intense burning sensation¹ and poisonous aftereffects.

¹ The burning sensation, which is similar to but more lasting than that produced by the oil from black mustard seed, was responsible for the name. The chief constituent of this natural oil is allyl isothiocyanate, $C_3H_5.NCS$.

ORGANOMETALLIC COMPOUNDS

14-10 Compounds in which a metallic atom and a carbon atom are linked *directly*¹ are called *organometallic*. Since there is no sharp dividing line between metals and the borderline metalloids, it is convenient to include within the definition elements of "somewhat metallic" properties, such as arsenic and silicon.

Two types are recognized. In *simple* organometallic compounds, the metallic atom is bound to carbon *only*, as in tetraethyllead, $(C_2H_5)_4Pb$. In those of the *mixed* type, the metal is bonded also to an electronegative element such as oxygen—*e.g.*, in the silicones and arsonic acids—or halogen, as in a Grignard reagent such as $H_3C.Mg.Br$. It has been noted already (Sec. 7-15) that ether solutions of Grignard reagents are actually equilibrium mixtures of simple and mixed organomagnesium compounds:

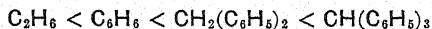


Equilibriums of this type are common among the organic compounds of other polyvalent metals such as zinc and cadmium.

The short dashes or periods used in the formulas of organometallic compounds are intended to show only the *order* in which different elements are joined. The *nature* of the bond between carbon and a metallic atom—which has much to do with the properties of the compound—varies widely. In some organometallic compounds, this bond appears to be almost purely covalent; others of these compounds are good conductors of electricity, when dissolved in suitable solvents, and have chemical properties which indicate that the bond is predominantly ionic. Polarity of the bond increases, as would be expected, with the electropositive nature of the metal, *e.g.*,



and with the electronegativity of the parent hydrocarbon, as in the series

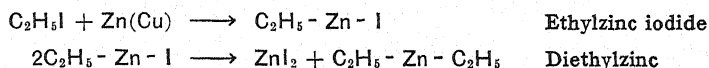


A few hydrocarbons, such as acetylene, contain hydrogen atoms acidic enough to be replaced by direct reaction with a metal (formation of

¹ Substantially any element except an inert gas may be present in some compound which also contains carbon—that is, it may be part of an organic compound. Various classes of compounds in which other elements are linked to carbon *indirectly*, through oxygen, sulfur, or nitrogen, have been mentioned already. The most numerous are the metallic *salts* of carboxylic and sulfonic acids and of other, less acidic organic compounds. Another class includes *esters* of acids such as H_3PO_4 and H_3AsO_4 , in which there are covalent linkages through oxygen. Linkage through nitrogen is found in the *amine salts* of acids such as $HAuCl_4$ and H_2PtCl_6 and in amine "double salts" with metallic chlorides, $SnCl_2$, $HgCl_2$, etc.

acetylides, Sec. 3-17), and some unsaturated hydrocarbons are able to add sodium or another very active metal at a C=C bond. But most organometallic compounds are obtained, either directly or indirectly, from alkyl halides. Three general methods are illustrated in the following section.

14-11 Alkylmetals; Aryllithiums; TEL. The first-known organometallic compound was prepared by Frankland (1849), who was seeking to obtain ethyl free radicals by heating ethyl iodide with a zinc-copper couple. Reaction occurs, in two stages, as follows:



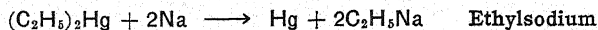
Diethylzinc is a nonconducting liquid boiling at 118°C. Both it and the dimethyl compound burn spontaneously in air but can be prepared and used in an atmosphere of nitrogen or carbon dioxide. Dimethylmagnesium burns even in carbon dioxide but is stable in nitrogen. Dimethylmercury, an extremely poisonous compound, is stable in air. In spite of the special difficulties and dangers involved, compounds of the types R_2Zn and R_2Hg were used frequently in organic syntheses, prior to 1900, for introducing their alkyl radicals into other compounds. They have since been displaced almost completely by the Grignard reagents, which always accomplish the same ends more conveniently and usually more effectively.

Frankland's method—heating an alkyl halide with a metal or an alloy—has been used widely for preparing organoderivatives of tin, cadmium, and many other metals. It is the basis of the present production of tetraethyllead (below); Grignard's discovery was an outgrowth.

The most general present method for preparing organometallic compounds depends on reactions of Grignard reagents with anhydrous metallic halides,¹ *e.g.*,

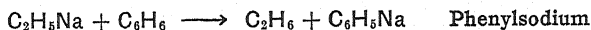


In a third method, a previously prepared derivative of one of the heavy metals, such as zinc or mercury, is treated with a more active metal, *e.g.*,

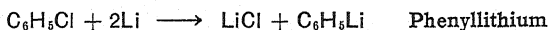


¹ The reaction with mercuric halides can be controlled to yield either R_2Hg or R.Hg.X . The latter—alkylmercuric halides—are stable compounds which can be recrystallized from water-ethanol solutions and usually have sharp melting points, *e.g.*, 129°C for $n\text{-C}_4\text{H}_9\text{Hg.Br}$. They are often prepared for the identification of primary and secondary alkyl halides by converting these into Grignard reagents and reacting with an excess of the corresponding mercuric halide (chloride, bromide, or iodide).

The product is a white powder which burns spontaneously in air. It can be used to obtain phenylsodium by the displacement

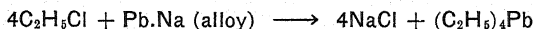


Aryllithium Compounds. Lithium, the least electropositive of the alkali metals, differs from the others in reacting with a number of halides, both alkyl and aryl, to give good yields of ether-soluble organolithium compounds. The halide is dissolved in anhydrous ethyl ether and heated with lithium shavings, *e.g.*,



The products may be used directly, in the ether solutions in which they have been prepared, for most of the same purposes as Grignard reagents. They are of special importance because chlorobenzene and similar unreactive aryl halides do not yield Grignard reagents.

Tetraethyllead, TEL, is the organometallic compound of greatest industrial importance. It is manufactured in very large quantities¹ for use as an antiknock agent in motor fuel (Sec. 6-6). Ethyl chloride is heated with a lead-sodium alloy and the organic product distilled off with superheated steam at 200°C:



Tetraethyllead is a heavy, colorless liquid (*d*, 1.659, b.p. 152°C at 291 mm). It is highly poisonous and requires special precautions in handling. This explains the warnings seen on most gasoline dispensing pumps.

14-12 Organosilicon Compounds; Silicones. The element silicon occurs just below carbon in the fourth group of the periodic table. It has four valence electrons, and its regular mode of reaction is to form four covalent linkages, *e.g.*, in silane, SiH_4 , and in silicon tetrachloride, SiCl_4 . Reactions of SiCl_4 with methylmagnesium halides yield methylchlorosilanes and tetramethylsilane:

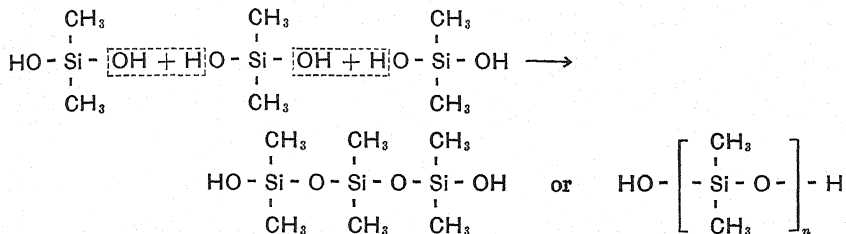


Such products are made industrially by passing the vapors of methyl chloride (or another alkyl chloride) through a heated mixture of silicon and powdered copper, which serves as a catalyst. The product is a mixture of CH_3SiCl_3 , $(\text{CH}_3)_2\text{SiCl}_2$, and $(\text{CH}_3)_3\text{SiCl}$; these are separated by fractional distillation.

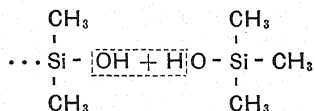
The methylchlorosilanes are readily hydrolyzed, even by stirring with water, the chlorine atoms being replaced by hydroxyl. The products are

¹ The first plant for the production of TEL by a *continuous* process is scheduled to begin operation in 1952 with a rated annual capacity of 50 million pounds. Total current production is estimated at twelve to fifteen times this figure.

not, however, simple molecules such as $(\text{CH}_3)_2\text{Si}(\text{OH})_2$ but condensation polymers formed by reactions of the type



The physical properties of the products depend largely upon the value of n , which can be controlled in various ways such as the temperature and other conditions of hydrolysis and polymerization. One way to obtain shorter chains is to hydrolyze a mixture of $(\text{CH}_3)_2\text{SiCl}_2$ and $(\text{CH}_3)_3\text{SiCl}$, which terminates them by the reaction



More complex structures, containing cross-linked chains (cf. Sec. 23-8), are obtained when CH_3SiCl_3 is present in the mixture hydrolyzed.

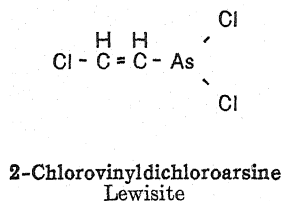
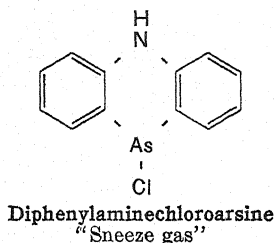
Silicones. All the products of the above reactions are known to the public as silicones. Their $\cdots \text{Si}-\text{O}-\text{Si}-\text{O}-\text{Si}-\text{O} \cdots$ chains are similar to those of the inorganic silicates and convey comparable stability upon the organosilicon compounds. These are produced with a wide range of physical properties. Silicone rubber is more resilient¹ than natural rubber and is valuable for such purposes as making gaskets which must stand temperatures and corrosive chemicals that would quickly destroy natural or synthetic rubber. Silicone oils show remarkably little viscosity change with temperature and are used as lubricants where extremes—either very high or very low—will be encountered. Silicone resins make excellent water-resisting and nonconducting coatings (*e.g.*, for insulators).

14-13 Organoarsenic Compounds. Phosphorus² and arsenic, in the fifth column of the periodic table, form many organic compounds analogous to corresponding types of nitrogen compounds. Those in which

¹ It is the "bouncing putty" of the toy stores and is also used as the core of golf balls, as well as for many industrial purposes.

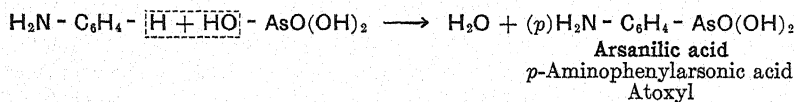
² The most important organic compounds of phosphorus are *esters* of phosphoric acid, H_3PO_4 , or of pyrophosphoric acid, $\text{H}_4\text{P}_2\text{O}_7$. Many such esters are involved in biochemical processes (Chap. 27). Triphenyl phosphate and tri-*o*-cresyl phosphate are industrial plasticizers.

arsenic is united directly to carbon are of greatest interest. These include the chemical-warfare agents

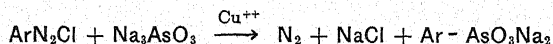


Diphenylaminechloroarsine is made by heating diphenylamine with arsenic trichloride. It is highly irritant to the nose and throat, producing sneezing and coughing but without permanent injury after moderate exposure. A mixture with tear gas (chloroacetophenone) in hand grenades is used by police for dispersing crowds. Lewisite is made by passing acetylene into arsenic trichloride in the presence of anhydrous AlCl_3 . The principal component is shown above. It is a powerful respiratory irritant and produces skin blisters similar to those of mustard gas; but the effect is quicker, more lasting, and more irritating. Tending to counterbalance these destructive uses, some organic compounds of arsenic are important medicinals.

14-14 Arsonic Acids; Arsonation. One class of useful organoarsenic drugs consists of aryl arsonic acids and their salts. These acids can be obtained by heating arsenic acid, H_3AsO_4 , with an amine or a phenol (that is, with an aromatic compound in which the *ortho* and *para* positions are sufficiently activated), *e.g.*,

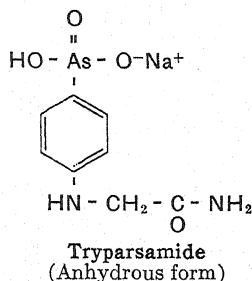
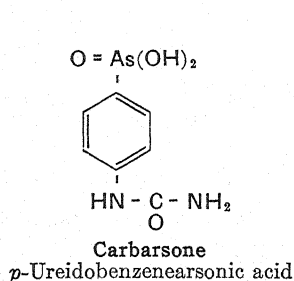


By analogy to sulfonation and other nuclear substitutions, this reaction is commonly known as *arsonation*. Better yields are usually obtainable by the action of sodium arsenite on a diazonium salt (Bart reaction):



The arsonic acids have a powerful destructive action against certain protozoa, and several are sufficiently harmless to man to permit their use in combatting such organisms *within* the human body. Carbarsone is

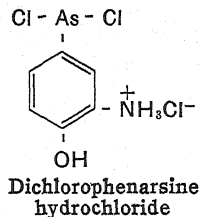
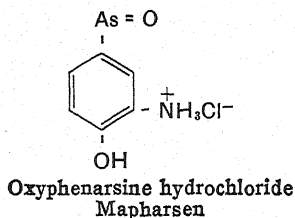
used extensively and effectively in amebic dysentery and tryparsamide in African sleeping sickness.



14-15 Antisymphilitic Drugs. The treatment of syphilis with organo-arsenic compounds has an interesting history which begins with the researches of Paul Ehrlich in the early part of this century. After long experimentation, in the course of which he prepared and tested atoxyl and various related arsonic acids, Ehrlich concluded that arsenic in the quinquavalent (pentavalent) condition is ineffective against the spirochete of syphilis. He then set about a carefully planned series of experiments designed to produce a useful drug containing arsenic in a reduced form. This effort was rewarded in 1910 by the production of Salvarsan, or "606." It is said that this was its number in the series of compounds prepared in slowly approaching his objective. Salvarsan (renamed arsphenamine in the United States) is a derivative of arsenobenzene, in which two substituted phenyl groups are joined through the $-\text{As}=\text{As}-$ linkage. Neoarsphenamine is a closely related compound which is more soluble and easier to administer.

The introduction of arsphenamine and neoarsphenamine revolutionized the treatment of syphilis. Both compounds were used widely for many years in spite of the objection that they are easily oxidized in solution to extremely toxic products. They have been deleted from the *United States Pharmacopeia*,¹ which lists oxyphenarsine hydrochloride and dichlorophenarsine as effective arsenicals. These are now supplemented by antibiotics (Chap. 27) in medical treatment.

¹The *United States Pharmacopeia* (USP) is an authoritative reference book which gives specifications for the purity and strength of what it describes as "the best and most important medicines and medical aids available." Substances listed therein are commonly called "official" by pharmacists and physicians. *New and Nonofficial Remedies*, an annual publication of the American Medical Association, gives additional information on the properties and uses of the more recent USP medicinals and describes some additional ones.



14.16 Chemotherapy means, literally, healing by chemistry. By convention the term is usually restricted to the administration of special classes of chemical compounds for the purpose of killing microorganisms *within the body* of a higher animal. In order to be used for this purpose, it is obvious that a substance must have properties quite different from those of phenol, mercuric chloride, and similar antiseptics used for sterilizing hands and instruments and even different from those which can be used locally for skin infections. The essential requirement is that the dose which can be tolerated by the patient shall be as large as possible in comparison with that required to kill the microorganism. The ratio between these doses is sometimes called the *therapeutic index*.

As just indicated, some arsenicals are effective against protozoan invasions and against the spirochete of syphilis. They are useless, however, against bacteria. Twenty-five years after Ehrlich produced Salvarsan, the introduction of the sulfa drugs made possible the first application of chemotherapy to bacterial infections. A few years later, these were supplemented by penicillin and other antibiotics.

Questions

1. (a) Compare the arylsulfonic acids with the aromatic carboxylic acids of about the same molecular weight with respect to melting points, volatility, solubility relations, and ionization. (b) How could you distinguish most quickly between benzoic acid and benzenesulfonic acid?
2. Considering the properties of the arylsulfonic acids, explain why it is often difficult to isolate them in pure condition.
3. Write structural equations for the major reactions which occur when: (a) *p*-toluenesulfonic acid is treated with a solution of sodium hydroxide; (b) the sodium salt of this acid is fused with sodium hydroxide; (c) β -naphthol is manufactured from 2-naphthalenesulfonic acid.
4. Write full structural equations for all reactions necessary in making *o*-toluic acid from toluene: (a) first sulfonating toluene; (b) first nitrating toluene.
5. Write structural equations for converting *p*-toluenesulfonic acid into its acid chloride, amide, and methyl ester by reactions similar to those regularly used for converting benzoic acid into its corresponding derivatives.
6. Insoluble sulfones, Ar_2SO_2 , are usually formed to a limited extent in the industrial sulfonation of aromatic hydrocarbons. Write a structural equation indicating how they arise.

7. Summarize the similarities and the difference in the structures of the three classes of compounds described in this chapter as synthetic detergents.

8. Explain why the presence of a base (sodium hydroxide or pyridine) is advantageous when benzenesulfonyl chloride is used to react with an amine.

9. Write an equation showing the probable mode of formation of diethyl sulfate by reaction between ethyl carbonium ion and sulfuric acid (cf. Sec. 8-11).

10. Define alcohols, ethers, carboxylic acids, and esters as *derivatives of water* and show that the corresponding thio compounds bear a like relationship to hydrogen sulfide.

11. Show the formula of the product you would expect to be formed when: (a) a carboxylic acid is esterified with a mercaptan; (b) a thioacid is esterified with an alcohol.

12. Write an equation illustrating: (a) a synthesis made possible by the use of phenyllithium; (b) a general method for making alkylmetals through the use of Grignard reagents.

13. Assuming an annual production of 600,000,000 pounds of tetraethyllead, calculate the quantities of metallic sodium and of ethyl chloride required if the yield is quantitative.

14. Write typical equations for condensations of the products formed when the methylchlorosilanes are hydrolyzed.

15. An organic compound dissolves in water, and in this solution BaCl_2 immediately produces a white precipitate insoluble in acids. (a) What element, other than C, H, O, and S, is almost certainly present? (b) Write the structural formula of a specific compound that would behave in this way.

16. A test for sulfur commonly applied to proteins consists in adding sodium hydroxide and lead acetate and boiling; in the presence of sulfur, the initially white precipitate of $\text{Pb}(\text{OH})_2$ turns brown or black. Explain, and suggest in what state of oxidation the sulfur is contained in proteins.

17. Write equations for the general reactions by means of which almost any sulfonic acid can be converted into a solid derivative, sparingly soluble, well crystallized, and of definite melting point.

REVIEW EXERCISES

1. **Relations between Properties and Structures.** Predict any significant differences which may be expected between the following compounds with respect to the properties indicated. Be prepared to cite a *general* rule on which your prediction is based or, lacking such a rule, to support your opinion by a pertinent laboratory observation or other information.

<i>Compounds for Comparison</i>		<i>Properties</i>
<i>n</i> -Octane	<i>n</i> -Octadecane	Boiling point
<i>n</i> -Octane	2,2,4-Trimethylpentane	Boiling point; antiknock quality
1-Pentene	<i>n</i> -Pentane	Solubility in cold H ₂ SO ₄
<i>n</i> -Hexane	2-Hexene	Speed of reaction with bromine
2-Pentene	2-Methyl-1,3-butadiene	Ease of polymerization
1-Pentyne	1,3-Pentadiene	Action with ammoniacal cuprous chloride
Gas oil	Natural gasoline	Volatility
<i>n</i> -Hexane	Benzene	Melting point
Toluene	<i>o</i> -Nitrotoluene	Density
Benzene	1-Hexene	Reactivity with dilute KMnO ₄ solution
Cyclohexane	Benzene	Activity in Friedel-Crafts reaction
Benzene	Nitrobenzene	Reactivity toward mixed acid
Toluene	<i>p</i> -Toluenesulfonic acid	Melting point
<i>p</i> -C ₆ H ₄ X ₂	<i>m</i> -C ₆ H ₄ X ₂	Melting point
Ethyl bromide	<i>n</i> -Amyl bromide	Boiling point; density
Ethyl bromide	Ethyl iodide	Density
<i>n</i> -Octane	1-Chlorooctane	Density
<i>n</i> -Butyl bromide	<i>n</i> -Octane	Solubility in cold H ₂ SO ₄
Ethyl iodide	Ethyl chloride	Dipole moment
<i>n</i> -Amyl bromide	<i>tert</i> -Amyl bromide	Tendency toward nucleophilic displacements
<i>n</i> -Butyl bromide	<i>p</i> -Bromotoluene	Reactivity toward hot NaOH solution
Benzyl chloride	<i>o</i> -Chlorotoluene	Reactivity toward AgNO ₃ solution
2-Pentanol	Ethanol	Miscibility with water
Ethanol	2-Octanol	Solvent power for octadecane
Methanol	1-Hexanol	Degree of association
1-Pentanol	<i>tert</i> -Amyl alcohol	Reactivity with cold concentrated HCl
Cyclohexanol	<i>p</i> -Cresol	Solubility in cold dilute NaOH
Ethanol	Ethyl ether	Solvent power for hydrocarbons
1-Octanol	<i>n</i> -Butyl ether	Boiling point
Ethyl ether	Butanol	Reactivity toward acetyl chloride
Ethyl ether	Petroleum ether	Solubility in cold sulfuric acid
Carbonic acid	β -Naphthol	Strength as acid
<i>o</i> -Cresol	Toluene	Reactivity with cold dilute KMnO ₄
Phenetole	Phenol	Solubility in cold dilute NaOH
Phenetole	Benzyl alcohol	Reactivity toward bromine
Anisole	α -Naphthol	Ferric chloride reaction

Compounds for Comparison		Properties
Benzyl alcohol	Benzoic acid	Ease of oxidation
Butyraldehyde	Methyl ethyl ketone	Reactivity toward Tollens's reagent
Propionaldehyde	<i>n</i> -Propyl alcohol	Molecular heat of combustion
Hexanoic acid	2-Hexanol	Solubility in cold dilute NaOH
Formic acid	Propionic acid	Ease of oxidation
Benzoic acid	Benzoyl chloride	Ease of reduction
<i>o</i> -Toluic acid	<i>o</i> -Cresol	Solubility in NaHCO ₃ solution
Benzoyl chloride	Benzyl chloride	Reactivity with ethanol
Ethyl bromide	Benzoyl chloride	Reactivity with phenol
Ethyl benzoate	Butyl benzoate	Saponification equivalent
Ethyl benzoate	Phenetole	Solubility in boiling NaOH
Butyric acid	Sodium butyrate	Conductivity of 0.05- <i>M</i> solution
<i>p</i> -Toluic acid	<i>p</i> -Toluenesulfonic acid	Solubility in water and in ether
<i>p</i> -Toluic acid	<i>p</i> -Toluenesulfonic acid	pH of 0.01 <i>M</i> solution
Butyryl bromide	<i>n</i> -Butyl chloride	Reactivity with ammonia
Benzyl chloride	Aniline hydrochloride	Reactivity toward AgNO ₃ solution
Benzamide	Benzyl amine	Stability of carbon-nitrogen linkage
<i>p</i> -Toluidine	Methylaniline	Reactivity in carbylamine test
Benzamide	Aniline	Solubility in cold, dilute HCl
Diethylamine	Diphenylamine	Strength as base
Benzamide	Ammonium benzoate	Reactivity toward cold, dilute NaOH
Acetanilide	Ethylaniline	Solubility in cold, dilute HCl
<i>o</i> -Toluidine	Benzyl amine	Behavior with cold nitrous acid
Solid KOH	Phosphoric anhydride	Suitability as drying agent for amines
Calcium chloride	Potassium carbonate	Suitability as drying agent for alcohols
Metallic sodium	Solid NaOH	Suitability as drying agent for alcohols
Solid KOH	Phosphoric anhydride	Suitability as drying agent for alcohols
Benzene	Kerosene	Suitability for cleaning lubricating oil from a flask

2. Distinctions through Characteristic Properties. Tell briefly but clearly how you could distinguish best between *pure* specimens of the following compounds through the use of one or more simple qualitative tests. Consult Section 3-23 and do not use numerical constants such as boiling and melting points. Describe accurately the observations, including *differences* in behavior, on which you would base your conclusions. In so far as possible, give for each compound a positive test to which the other(s) would respond negatively or differently.

- $C_4H_9.O.C_4H_9$ and $CH_3.(CH_2)_6.CH_3$
- $C_2H_5.CO.CH_3$ and $CH_3.CH_2.CH_2.CHO$
- $C_6H_5.CH_3$ and $C_6H_5.Br$, with and also *without* the use of a chemical reaction
- $C_2H_5.O.C_2H_5$ and $CH_3.CH_2.CH_2.CH_2.OH$
- $H_3C.C_6H_4.NH_2$ and $C_6H_5.NHCH_3$
- $H_3C.C_6H_4.CH_2Cl$ and $CH_3.CH_2.C_6H_4.Cl$
- $C_3H_7.O.C_3H_7$ and $C_2H_5.CO.C_2H_5$
- $C_6H_5.C \equiv CH$ and $C_6H_5.CH = CH_2$
- $H_3C.C_6H_4.COOH$ and $C_6H_5.CO.OCH_3$
- $C_6H_5.CH_3$, $CH_3.C_6H_4.OH$, $C_6H_5.O.CH_3$, $C_6H_5.COOH$, and $C_6H_5.CH_2OH$

3. Summary of the General Reactions. Review and correlate the general methods for preparing organic compounds, in so far as they have been considered in Chapters 1 to 14, by constructing two charts, as follows:

(a) Starting with ethylene or ethyl alcohol and using structural formulas throughout, diagram all the important general methods through which the major types of *aliphatic* compounds can be *prepared* and *converted one into another*. Include methods for lengthening and shortening carbon chains. Do not employ reactions—such as the chlorination of an alkane—which occur but cannot be controlled or directed to give a reasonable yield of an individual product.

(b) Starting with benzene, construct a similar chart showing the important synthetic relations among the major types of *aromatic* compounds. Include methods for interconversions between aliphatic, alicyclic, and aromatic compounds.

Suggestions. Set out with the objective of preparing accurate “road maps” which will show clearly the most direct *feasible* routes for passing from a compound of a given type to a product of any other type. Indicate, on lines connecting the formulas of compounds, the reagents and conditions essential for the reactions. One type of diagram is suggested by Figure 23-2; individual students often develop modifications which they find preferable for their own use. Plan carefully in order to avoid undue crowding in some regions. Cardboard sheets about 22 by 28 inches are satisfactory and desirable for the finished charts. The latter provide an over-all view of much material which has been learned piecemeal and a useful summary of many chemical properties. Students who prepare them carefully—and independently—find the exercise invaluable for review and preparation for examination.

4. Applications of the General Reactions. Show by structural equations how the following syntheses can be effected by means of general reactions. Most of them require the consecutive use of two or more reactions; or it may be necessary to divide the original substance and convert each part into another compound, the products being finally reacted with each other. Use *inorganic* reagents (including carbon dioxide and sodium cyanide) as desired. Use no organic compound other than those mentioned (except that anhydrous ethyl ether may be considered available for use as a solvent).

Prepare: (a) *n*-hexane from *n*-propyl alcohol by two different methods; (b) *n*-hexane from *n*-hexyl alcohol; (c) an isomer of *n*-hexane from acetone; (d) *n*-hexane from *n*-heptanoic acid; (e) a cyclohexadiene from 1,6-dibromohexane; (f) *sec*-butyl alcohol from *n*-butyl alcohol; (g) 2-pentanol from a lower aldehyde; the use of a lower alcohol is also permitted (cf. Sec. 10-6); (h) benzyl ether from benzyl alcohol (not by dehydration); (i) 3-pentanol from propionic acid; (j) valeronitrile from butyraldehyde; (k) isobutyric acid from acetone by two methods; (l) phenetole from benzene and ethylene; (m) ethyl *n*-butyrate from acetaldehyde (Sec. 10-9); (n) isobutyl isobutyrate from isobutyric acid; (o) acetic anhydride from acetylene, via acetaldehyde; (p) isopropyl propionate from ethyl and methyl alcohols; (q) benzylammonium bromide from phenylacetic acid; (r) *p*-iodotoluene from *p*-nitrotoluene; (s) α -naphthoic acid from naphthalene; (t) benzyl benzoate from benzaldehyde by the most direct method; (u) benzanilide from benzene.

CHAPTER 15

POLYFUNCTIONAL ALIPHATIC COMPOUNDS

ALKENE DERIVATIVES AND POLYHALIDES

Preceding chapters have dealt mainly with the hydrocarbons and those simple derivatives which contain a *single* functional group. This chapter and those which follow describe compounds containing two or more functional groups. Depending on whether these groups are the same or different, the substances are called *polysubstituted* or *mixed* compounds.

Varied combinations of functional groups in the same molecule and opportunities for position and chain isomerism combine to make theoretically possible an almost infinite number of polysubstituted and mixed compounds (Table 15-1). Tens of thousands are actually known, and many are of considerable interest either as industrial products or on account of their biochemical relations.

TABLE 15-1 CALCULATED NUMBERS OF ISOMERS POSSIBLE

Type of compound	Isomers theoretically possible if	
	C = 5	C = 10
Hydrocarbons, C_nH_{2n+2}	3	75
Monosubstitution products, $C_nH_{2n+1}.X$	8	507
Disubstitution products, $C_nH_{2n}.X_2$	21	2,261
Mixed disubstitution products, $C_nH_{2n}.XY$	31	3,959

Chapters 15 through 21 deal mainly with the polysubstituted and mixed derivatives of aliphatic hydrocarbons. The polyfunctional aromatic compounds of major interest are surveyed in Chapters 23 and 24 from the standpoint of their relationship to the hydrocarbons—benzene, toluene, naphthalene—from which nearly all of them are produced.

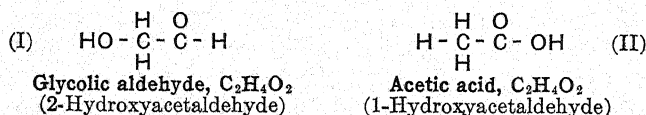
15-1 General Principles. The major functional groups already studied are: the ethylenic double bond ($C=C$), halogen atoms (Cl, Br, I), and OH, $C=O$, $COOH$, NO_2 , NH_2 , and SO_3H . It has been shown that these can be introduced into organic molecules by *general methods*, applicable to the preparation of all or most members of any series. Each group has its own characteristic reactions, resulting in the common chemical properties of the compounds that contain it. Each, likewise, has its own rather well-defined effects upon physical properties such as boiling point,

density, and solubility relations. Familiarity with these reactions and relations makes it possible to predict with considerable accuracy the essential properties, both physical and chemical, of many polysubstituted and mixed compounds. This depends upon the fact that, when two or more functional groups are present in the same molecule, it is often safe to predict that *each* will act much as it would if present alone.

This *rule of the independent action of functional groups* is the most profitable approach to the study of polysubstituted and mixed organic compounds. Obviously it requires and affords a review of the general synthetic methods and the typical reactions of the characteristic groups. It allows the omission of much detail and repetition, permitting the more adequate treatment of principles. Most important of all, it provides in large measure for the substitution of logic for memory.

Important as it is, the rule of the independent action of functional groups is too broad and too beautifully simple to be entirely accurate. Strictly speaking, it is *never* accurate, for when two groups are present in the same molecule, each always influences the other to a certain extent. Fortunately, however, most of these effects are minor and may be neglected—in fact they *should* be neglected, in order not to obscure the much more important information made available by applying the rule.

15.2 Mutual Influences. The rule of independent action holds most accurately when functional groups in a molecule are well separated. Conversely, important exceptions are most probable when the groups are so situated as to permit some kind of interaction (by resonance or otherwise). Such interaction is always to be expected, for example, when two functional groups are attached to the *same* carbon atom. Reference has been made already to the spontaneous elimination of water which nearly always occurs when two hydroxyl groups are attached in this way. The following is another illustration. Behaving quite according to the rule, glycolic aldehyde (I) gives the reactions expected of an aldehyde and also those of a primary alcohol. But the isomeric compound (II), in which the hydroxyl group is attached to the carbonyl carbon, gives few reactions suggestive of either. Instead, we encounter the entirely different set of properties characteristic of the *carboxylic acids*.

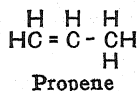
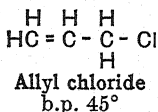
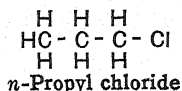


This is one of the most striking results of “mutual influences” within molecules, though one which has become so familiar that it ceases to appear remarkable.

Many applications of the rule of independent action will be given in what follows. The student is expected to apply it to the prediction of physical and chemical properties in many of the questions which follow the several chapters—an essential feature of the method of study which is here adopted. For the most part, the text will concentrate on pointing out major exceptions to the rule and, in so far as possible, explaining them.

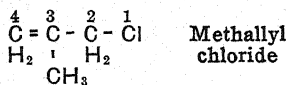
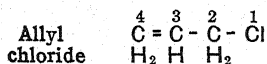
UNSATURATED HALOGEN COMPOUNDS

15.3 Allyl Chloride. The chemical reactions of allyl chloride are readily predictable from its structural relations to propene and to propyl chloride:



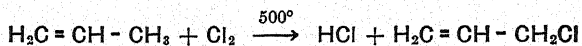
Like propene and under similar conditions it readily adds hydrogen, chlorine, bromine, hydrogen halides, etc., and promptly reduces permanganate solutions. Like propyl chloride it enters into the various replacement reactions of the alkyl halides, through which it is used to introduce the allyl radical into other organic compounds.

The only unexpected property of allyl chloride is the exceptional *ease* of these halogen replacements, which proceed many times as fast as with *n*-propyl chloride under parallel conditions. This special reactivity is found in other unsaturated halides in which the C=C bond is situated in the 3,4 position with respect to the halogen atom:



If the double bond is more remote, no significant increase in reactivity is observed.

Allyl chloride can be prepared from allyl alcohol, $\text{H}_2\text{C}=\text{CH}.\text{CH}_2\text{OH}$, by the general methods for replacing hydroxyl by halogen (Sec. 7.4). It is now manufactured extensively by a special method, the high-temperature chlorination of propene:



Yields of 80 per cent or better are reported under industrial conditions, in spite of the fact that propene *adds* chlorine readily at ordinary and moderate temperatures. The main objective is the manufacture of

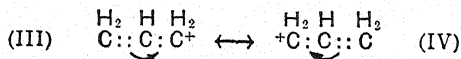
glycerol from allyl chloride (Sec. 16·10), but the process has also made available allyl alcohol, allyl ether, and other related compounds.

15·4 Allyl chloride exchanges chlorine for iodide 79 times as fast as *n*-propyl chloride by reaction with potassium iodide in acetone. In a comparable experiment with sodium thiosulfate, allyl iodide released its halogen atom 120 times as fast as *n*-propyl iodide. There is strong evidence that these reactions—and several others in which allyl halides show exceptional reactivity—are nucleophilic displacements proceeding through a transition state (Sec. 7·9). What we need to explain, therefore, is why the halogenated carbon, C¹, of an allyl halide is so much more susceptible to a back-side attack by nucleophilic ions.

The most reasonable explanation is based on the *polarizability* (Sec. 3·8) of the double bond. It assumes that the approach of a negative ion (such as I[−] or OH[−]) toward the back side of C¹ in allyl chloride (I) causes an electron shift in the direction indicated in (II). Such a displacement would favor the closer approach of the displacing ion to C¹ and increase the speed with which chloride is displaced by iodide. In the absence of a double bond, no such electron displacement is possible in *n*-propyl chloride. (Nor is there enhanced reactivity when a double bond is present, but in a position more remote from the halogen atom than in allyl halides.)



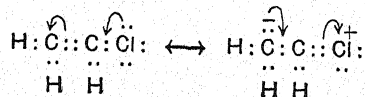
The allyl halides also show exceptional reactivity in reactions which proceed through the immediate removal of halogen and formation of the allyl carbonium ion. This is less difficult to explain. The carbonium ion, if formed, would be highly stabilized by resonance between the equivalent extreme forms:



Thus the formation of this ion would be favored. The formation of a carbonium ion probably explains, also, many so-called *allylic* rearrangements in which a compound of the general structure (V) is readily converted, more or less completely, into (VI):



15·5 Vinyl chloride, H₂C=CHCl, is peculiarly *inert* toward reagents which readily displace the halogen atom in allyl and in alkyl halides. This low reactivity of the chlorine atom is ascribed to stabilization of the molecule by resonance between the extreme forms:

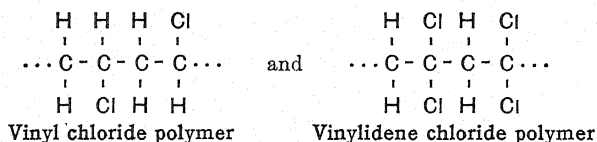


Physical evidence for resonance is found in the bond lengths measured by X-ray diffraction. The carbon-carbon bond is 1.38 Å, or slightly

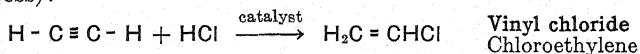
longer than the 1.34 Å of a typical C=C bond; the carbon chlorine distance is shortened to 1.69 Å, as against the 1.76 Å observed in ethyl chloride.

This low reactivity is encountered also in chloroprene (Sec. 6-17) and other compounds in which a halogen atom is attached directly to a carbon atom of the C=C bond.¹ Hence, such compounds are of little value in the ordinary synthetic reactions of the alkyl halides. Conversely, vinyl chloride and chloroprene polymerize with exceptional ease and find major applications in the form of high polymers.

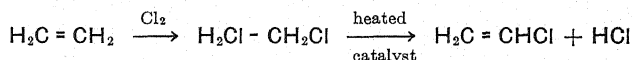
15-6 Vinyl Polymers. Addition polymerization is a reaction characteristic of compounds containing the vinyl grouping, $H_2C=C$. It usually occurs most readily if an electrophilic atom or group is attached to the second carbon atom. Thus vinyl chloride and vinylidene chloride, $H_2C=CCl_2$, polymerize much more easily than ethylene. Peroxides are very effective catalysts, and the reaction is usually regarded as proceeding through a free-radical mechanism (Sec. 6-16). The resulting high polymers are long, slender molecules with the repeating structures:



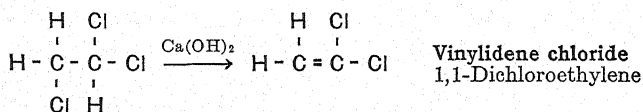
Monomeric vinyl chloride is manufactured from acetylene by the regulated addition of hydrogen chloride (acetylene being kept always in large excess):



It is produced even more extensively from ethylene by the sequence



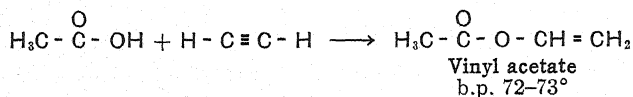
Vinylidene chloride is manufactured by the reaction



The trichloroethane required can be made either by the regulated chlorination of $CH_2Cl.CH_2Cl$ or by addition of chlorine to vinyl chloride. Calcium hydroxide as hot milk of lime is a favorite agent for the regulated dehydrohalogenation of polyhalides.

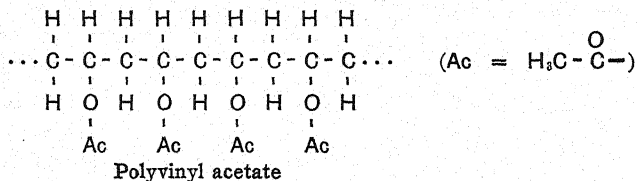
¹ The low reactivity of chlorobenzene, already noted, is comparable to that of vinyl chloride and has a like origin (Sec. 22-9).

Vinyl acetate, a third monomer widely used, is manufactured by the catalytic addition of acetic acid to acetylene:

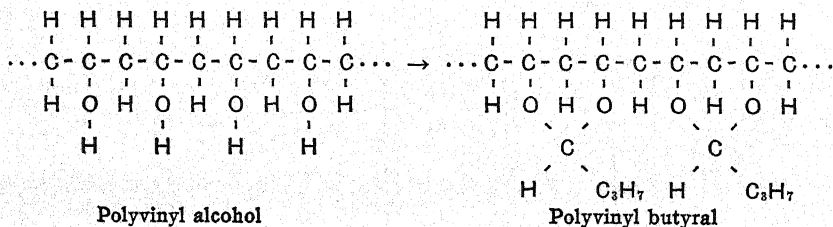


Each of these monomers can be polymerized separately; frequently, however, more satisfactory products are obtained by copolymerizing two of them in suitable proportions. Collectively, the vinyl polymers and copolymers form one of the major groups of synthetic plastics (Table 24-2). Trade names include Vinylite, Koroseal, and Geon. They are used for a wide variety of purposes such as the manufacture of rigid sheets and tubing, wire and cable coatings, flexible sheets and film, molded objects (*e.g.*, Vinylite phonograph disks), and protective coatings of various kinds including waterproofed cloth. Vinyon is a synthetic textile fiber consisting of vinyl chloride copolymerized with about 12 per cent of vinyl acetate; Dynel, another, is a copolymer with 40 per cent of acrylonitrile. Saran is vinylidene chloride copolymerized with a small amount of vinyl chloride; it is used mainly for extruded products such as tubing and artificial fibers and is characterized by great resistance to chemicals and other destructive agents.

Polyvinyl Alcohol; Vinal. Monomeric vinyl alcohol, $\text{H}_2\text{C}=\text{CHOH}$, is unknown (Sec. 20-13), but its polymeric form is manufactured by hydrolyzing off the acetyl groups of polyvinyl acetate:



Polyvinyl alcohol, as such, has some uses in the plastics industry, but its major use is based on the ability which it shares with simple alcohols to react with aldehydes and form acetals. For example, reaction with butyraldehyde gives polyvinyl butyral:



This is Vinal, which is used more than any other material as the inter-layer in safety glass.

15-7 Thermoplastics. Materials which soften when heated, and thus may be shaped, molded, or drawn into filaments, are described as thermoplastic.¹ Glass is the most familiar inorganic example. The vinyl and acrylate polymers described in this chapter are among the synthetic organic thermoplastics. A characteristic common to these materials is the long, slender, stringlike structure of their molecules. Thermoplasticity is associated with the ability of such molecules to slip over each other. (The very different behavior of cross-linked molecules is discussed in Section 23-8.)

Plastic materials differ widely in their hardness when cold and in the temperatures at which they soften enough to be worked. With a given monomer this can be controlled to some extent by regulating the degree of polymerization; in general, the working temperature rises with the degree of polymerization, and solubility in acetone and similar solvents decreases. Copolymerization affords an even more effective means for varying physical properties. A third method consists in incorporating into a molding powder a suitable soft solid or high-boiling liquid called a plasticizer (Sec. 24-11). For example, polymeric vinyl chloride is a hard, horny substance which softens somewhat on heating but is still too hard to work easily at temperatures short of decomposition; for this reason most articles molded from it contain 25 to 50 per cent of a plasticizer.

15-8 Unsaturated polyhalides are produced from acetylene by a combination of addition and elimination reactions as outlined in Figure 15-1. Both these and the saturated polyhalides resemble the parent hydrocarbons and the alkyl halides in being practically insoluble in water and in sulfuric acid and in their miscibility with nonpolar liquids. Boiling points and densities increase as expected with the number of halogen atoms in the molecule. Two properties not conspicuous in the alkyl halides become prominent with increasing halogen content. Inflammability decreases sharply; $\text{CHCl}=\text{CCl}_2$ and $\text{CCl}_2=\text{CCl}_2$ are rated as non-

¹ The dictionary meaning of the adjective *plastic* is pliable. The organic polymers which have this property when hot—polyvinyl chloride, polyacrylonitrile, cellulose acetate, polystyrene, etc.—are properly called synthetic resins. But the terms resin and plastic have come to be used practically interchangeably as nouns. Innumerable articles manufactured from these materials are known to the general public as “plastics,” although many of these are made of thermosetting resins (Sec. 23-8), and the item purchased is no longer plastic in the dictionary sense.

Both glass and the organic synthetic resins are noncrystalline materials, more accurately described as supercooled liquids than as solids. They have no definite melting points but soften progressively over wide ranges of temperature. A true solid—which is crystalline—changes little with rise in temperature until its melting point is reached, when it passes abruptly into the liquid state.

inflammable and are, therefore, much safer solvents than hydrocarbons. Biological activity is often marked and, in general, excessive inhalation of the vapors and contact with the skin are to be avoided. Perchloroethylene is used medicinally to destroy or expel intestinal worms; various other biological effects of polyhalides will be mentioned elsewhere.

Trichloroethylene and perchloroethylene have high solvent powers for fats, oils, waxes, etc., and dissolve natural and synthetic rubbers appre-

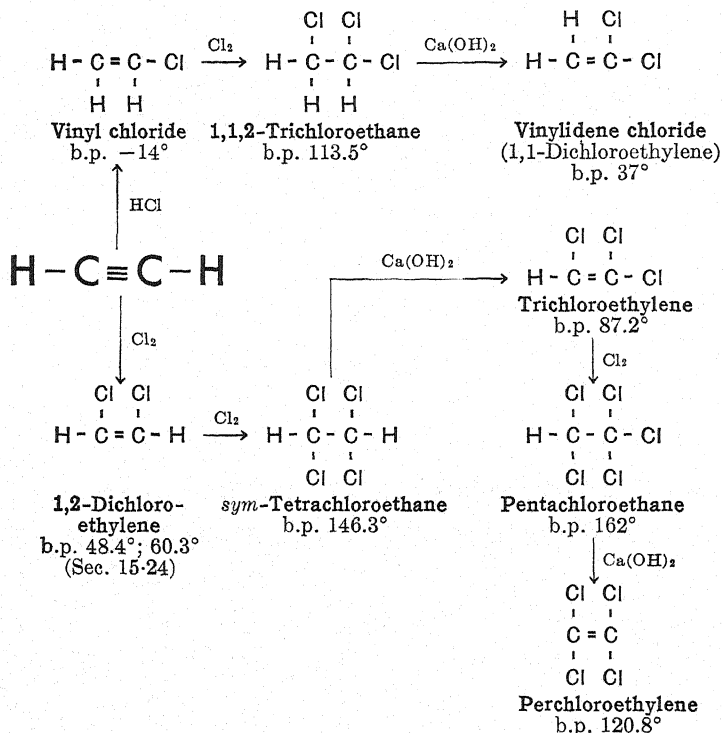


FIG. 15-1 Some halogen compounds produced from acetylene.

ciably. Large quantities of both are consumed as industrial solvents in metal degreasing, dry cleaning, and extracting oils from seeds (soybeans, cotton seed, etc.). The more inflammable 1,2-dichloroethylene is used for similar purposes when a lower boiling solvent is needed.

The polychlorides described here, in all of which the halogen atoms are attached directly to the $\text{C}=\text{C}$ group, resemble vinyl chloride in their inertness toward halogen replacements. They have less tendency than saturated polyhalides such as $\text{CHCl}_2\cdot\text{CHCl}_2$ to split out corrosive HCl ; this is one reason they are preferred as industrial solvents.

Rate of Addition Reactions. Trichloroethylene and perchloroethylene enter extremely slowly into the usual ethylenic addition reactions; they are easily mistaken for saturated compounds in the bromine-addition test for unsaturation. This behavior is generally observed if several electrophilic groups (*e.g.*, COOH, C₆H₅, halogen atoms) are joined directly to the C=C atoms. Some such compounds fail entirely to add halogen. Conversely, tetramethylethylene, (CH₃)₂C=C(CH₃)₂, adds bromine fourteen times as fast as ethylene.

These facts are consistent with what would be expected from the addition mechanism described in Section 3-8. A proton or other electropositive atom or ion is regarded as leading the attack and combining with a carbon atom on which an electron pair is most readily available. Electron-releasing methyl groups increase electron density on the C=C atoms and favor such an attack; electrophilic groups about these atoms have the opposite effect.

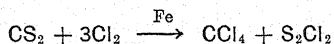
SATURATED POLYHALIDES

15-9 Methane polyhalides (Table 15-2) constitute a somewhat special class of compounds because their molecules contain only one carbon atom. They are usually made by specific rather than general methods. In general they are rather inert toward chemical changes; they cannot lose HX on treatment with alkalis, and most of the usual halogen replacements proceed slowly if at all.

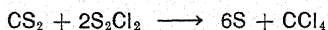
TABLE 15-2 IMPORTANT METHANE POLYHALIDES

Common name	Formula	Melting point, °C	Boiling point, °C	Density
Methylene chloride.....	CH ₂ Cl ₂	- 96.7	40.1	1.336
Freon-12.....	CCl ₂ F ₂	-155.	-29.2	1.486 ^{-30°}
Chloroform.....	CHCl ₃	- 63.5	61.2	1.489
Carbon tetrachloride.....	CCl ₄	- 22.6	76.8	1.595
Bromoform.....	CHBr ₃	7.8	150.5	2.890
Iodoform.....	CHI ₃	119	dec.	4.1

Carbon tetrachloride is manufactured principally by chlorinating carbon disulfide in the presence of a catalyst:



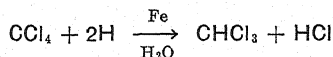
The by-product S₂Cl₂ (sulfur monochloride) is utilized in the further reaction:



The largest single use of carbon tetrachloride is for the manufacture of Freon-12. A major use is in fire extinguishers; this depends on the ease

with which the liquid is volatilized by a flame to form a blanket of heavy, noninflammable vapors which cut off access of air. Carbon tetrachloride is used extensively in dry cleaning and as a miscellaneous solvent for fats and related compounds. Its toxicity to lower organisms is utilized in the fumigation of stored grain.

Chloroform is usually manufactured from acetone or ethyl alcohol by the haloform reaction (below). Some is also produced in the chlorination of methane and through the regulated reduction of carbon tetrachloride, by stirring with powdered iron and water containing a little hydrogen chloride:

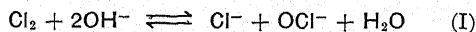


Chloroform is an excellent solvent, and most of its present uses (*e.g.*, for the extraction of penicillin, Sec. 27·27) are based on this property. It was the first general anesthetic used in surgery (by Simpson of Edinburgh, 1847) but has now been largely displaced by ethyl ether, which is less dangerous.

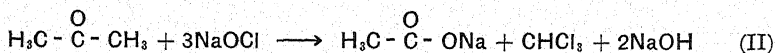
Iodoform differs from most other aliphatic halides in that it is *colored* (yellow) and a *solid* (hexagonal plates); its high density, 4.1, is also noteworthy. All these properties are associated with the fact that the heavy element iodine makes up 95 per cent of the molecule. Iodoform is an antiseptic and was formerly much used as such; it has now been largely replaced by substitutes which lack its penetrating odor and are more effective. It is made from ethyl alcohol or acetone by the haloform reaction.

The *Freons* are described in Section 15·14.

15·10 Haloform Reaction. Chloroform, bromoform, and iodoform can be made from acetone by reactions with alkaline hypohalite solutions. These reagents are prepared by dissolving chlorine, bromine, or iodine in a solution of sodium hydroxide or other strong base, *e.g.*,



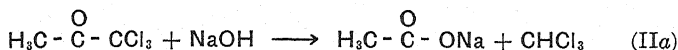
Such an alkaline hypochlorite solution yields chloroform readily by the over-all reaction



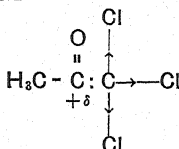
Similarly, hypobromites and hypoiodites yield bromoform and iodoform, respectively.

It is now well established that this *haloform* reaction occurs in two distinct stages—halogenation and chain cleavage. In the first stage of the hypochlorite reaction with acetone, the hydrogen atoms of one CH_3

group are replaced—stepwise—by chlorine, forming¹ trichloroacetone, $\text{H}_3\text{C}.\text{CO}.\text{CCl}_3$. (The remarkable ease with which halogens—including iodine—substitute in this reaction is discussed in Section 20·20, paragraph 3.) The second stage, which follows immediately upon the first, is alkaline cleavage:



The ease with which this cleavage occurs is likewise unusual. The weakening of the carbon-carbon bond which it discloses is ascribed to electron attraction by the chlorine atoms. This places an exceptionally high $+\delta$ charge on the carbonyl carbon



and renders it highly susceptible to nucleophilic attack by OH^- ions. Thus the carbanion $-\text{:CCl}_3$ is displaced and, stabilizing itself by the addition of a proton, forms the observed product, HCCl_3 . (The other product is acetate ion.)

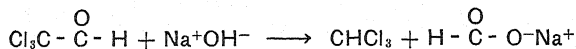
Scope of the Reaction. The haloform reaction occurs with all *methyl* ketones, $\text{R}.\text{CO}.\text{CH}_3$, and with all secondary alcohols of the type $\text{R}.\text{CHOH}.\text{CH}_3$, which are oxidized to methyl ketones by the hypohalite reagent. Only one aldehyde ($\text{CH}_3.\text{CHO}$) and one *primary* alcohol ($\text{H}_3\text{C}.\text{CH}_2.\text{OH}$) respond. The reaction has many applications in the preparation of carboxylic acids for through it either $\text{R}.\text{CO}.\text{CH}_3$ or $\text{R}.\text{CHOH}.\text{CH}_3$ can be converted into $\text{R}.\text{COOH}$.

The iodoform test is useful in identification because it differentiates between compounds which do and those which do not possess the structure just described; for example, it is positive with $\text{CH}_3.\text{CHOH}.\text{CH}_3$ but negative with its isomer $\text{CH}_3.\text{CH}_2.\text{CH}_2.\text{OH}$. The test is usually performed by adding a solution of iodine and potassium iodide to a warm, alkaline solution of the substance to be tested, and allowing to stand. Iodoform is readily recognized by its odor and by its distinctive, hexagonal, yellow crystals.

15·11 Chloral, $\text{Cl}_3\text{C}.\text{CHO}$, trichloroacetaldehyde, was first prepared by Liebig (1832) in the course of an investigation of the action of chlorine

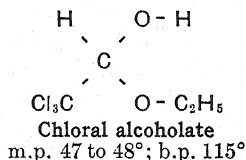
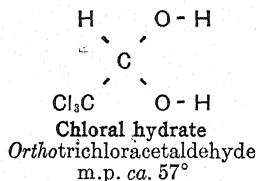
¹ Trichloroacetone, a well-known substance, cannot be isolated when acetone is treated with a hypochlorite. Trihaloketones have been obtained, however, when certain substituted-aryl methyl ketones are so treated. In a few instances it has been possible to isolate the successive products $\text{Ar}.\text{CO}.\text{CH}_2\text{X}$, $\text{Ar}.\text{CO}.\text{CHX}_2$, and $\text{Ar}.\text{CO}.\text{CX}_3$.

on ethyl alcohol. It is still made in that way. The net result of a complex series of reactions is oxidation of $\text{CH}_3\text{CH}_2\text{OH}$ to CH_3CHO and substitution of three chlorine atoms in the methyl radical. The product is an oily liquid (b.p. 98.1°C ; d , 1.512), which polymerizes spontaneously and is easily split by alkalis:



Nitric acid oxidizes it smoothly to trichloroacetic acid.

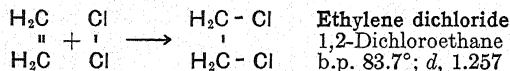
Chloral is noteworthy for the special ease with which it enters into all the addition reactions of carbonyl compounds. When mixed with about one-fifth its weight of water, there is formed promptly a crystalline mass of *chloral hydrate*. This is one of the few *orthoaldehydes* stable enough to be isolated. It melts without decomposition, but the molecule of water is split out at the boiling point and by the action of strong dehydrating agents (*e.g.*, cold sulfuric acid).



Chloral also differs from most other aldehydes in giving a stable *hemiacetal*, chloral alcoholate. Further reaction with ethanol gives the ordinary acetal, $\text{Cl}_3\text{C}.\text{CH}(\text{OC}_2\text{H}_5)_2$.

Chloral hydrate is sometimes used medicinally as a hypnotic. The very extensive use of chloral itself in the manufacture of DDT is described in Section 23-6.

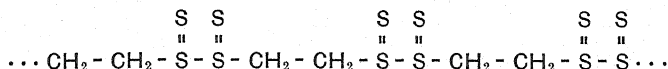
15-12 Ethane Dihalides. The symmetrical compound, 1,2-dichloroethane, usually called *ethylene dichloride*, is manufactured in large amounts by the addition of chlorine to ethylene:



Its major uses are as an industrial solvent and for chemical syntheses. Both chlorine atoms enter readily into the replacement reactions of the alkyl halides; for example, the following compounds are made by reactions with ammonia, sodium cyanide, benzene with AlCl_3 , and sodium acetate, respectively:

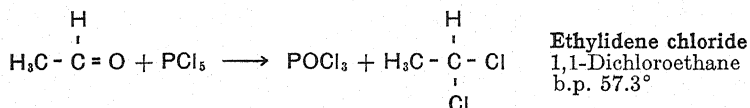
$\text{H}_2\text{N} - \text{CH}_2 - \text{CH}_2 - \text{NH}_2$	Ethylene diamine
$\text{NC} - \text{CH}_2 - \text{CH}_2 - \text{CN}$	Succinic nitrile
$\text{C}_6\text{H}_5 - \text{CH}_2 - \text{CH}_2 - \text{C}_6\text{H}_5$	1,2-Diphenylethane
$\text{CH}_3\text{CO.O} - \text{CH}_2 - \text{CH}_2 - \text{O.COCH}_3$	Ethylene glycol diacetate

Heated with sodium polysulfide, ethylene dichloride yields the synthetic elastomer Thiokol, which appears to have the repeating structure



Ethylene dibromide (b.p. 131.7°C) is made by the addition of bromine to ethylene. It is useful in laboratory syntheses based on replacements of the bromine atoms, but its largest use is in ethyl fluid for gasoline (Sec. 6-6).

Ethylidene chloride, 1,1-dichloroethane, is the major product when ethane is dichlorinated. It was first obtained by the reaction



Ethylidene chloride is—in sharp contrast with its isomer—of very limited value in chemical syntheses; most of the usual reagents for the displacement of halogen atoms either have no effect, or cause the elimination of hydrogen chloride, or yield complex products.

15-13 Dihalides of higher alkanes may have the halogen atoms joined to adjacent carbon atoms, to separated carbon atoms, or to the same carbon atom.

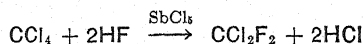
Those of the first type (*e.g.*, $\text{H}_3\text{C}.\text{CHCl}.\text{CHCl}$) are most important because they are readily prepared by addition of chlorine or bromine to alkenes. Those in which the halogen atoms are farther separated can be made from the corresponding dihydric alcohols when these are available, or by special methods (*e.g.*, production of $\text{CH}_2\text{Cl}.\text{CH}_2.\text{CH}_2.\text{CH}_2\text{Cl}$ from furfural, Sec. 26-10). The compounds of both these types are useful in syntheses depending on halogen replacements.

Compounds in which two halogen atoms are attached to the *same* carbon are much less important. The halogen atoms are generally unreactive, as in $\text{CH}_3.\text{CHCl}_2$, and the only general method of preparation is the action of phosphorus pentahalides on aldehydes and ketones.

15-14 Organic Fluorides; Freons. Monofluorides such as $\text{C}_2\text{H}_5\text{F}$ are quite unstable, having a marked tendency to split out hydrogen fluoride

and readily hydrolyzing. They are of minor interest only and of no present importance.

Interest in organic polyfluorides was aroused about 1930 when CCl_2F_2 , dichlorodifluoromethane, was produced commercially. The boiling point of this compound (-29.2°C) and the other properties mentioned below make it especially suitable for use as the cooling agent in domestic refrigerators and in air-conditioning units. Large quantities are now manufactured and used for this purpose under the trade name Freon-12. It is made from carbon tetrachloride by the reaction



Freon-12 will not burn, it is practically odorless, and appears to have no effect whatever on living organisms; mice have lived healthily for months in an atmosphere in which half of the nitrogen was replaced by CCl_2F_2 . It is unaffected by prolonged exposure to hot fuming nitric acid. It can be bubbled through melted sodium without tarnishing the metal—thus showing that the fluorine atoms are tightly held and also increase the stability of the carbon-chlorine bonds. Various other chloro-fluoro derivatives of methane and ethane are now manufactured (CCl_3F , CHCl_2F , CHClF_2 , $\text{CCl}_2\text{F.CClF}_2$, $\text{CClF}_2.\text{CClF}_2$, etc.) and sold under the family trade name Freon, with distinguishing numerals attached. Their properties are similar to those of Freon-12.

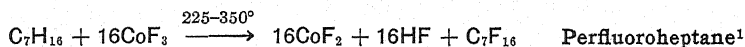
The inertness of Freon-12 is characteristic generally of compounds in which fluorine atoms (or fluorine and chlorine) are attached to the *same* carbon atom. Fluoroform, HCF_3 , has none of the anesthetic quality of chloroform. Trifluorotoluene, $\text{C}_6\text{H}_5.\text{CF}_3$, is extremely resistant to oxidation and, when this occurs, it is not the side chain which is attacked but the aromatic nucleus; the principal product is trifluoroacetic acid, $\text{F}_3\text{C.COOH}$. The plastic Teflon, polymerized $\text{F}_2\text{C}=\text{CF}_2$, is one of the most resistant of all such materials to heat and to chemical agents; Teflon tubing is used to handle extremely corrosive substances, including elementary fluorine. The addition polymerization of $\text{F}_2\text{C}=\text{CF}_2$ is noteworthy as the one important exception to the general rule that the monomer must contain the $\text{H}_2\text{C}=\text{C}$ group.

15-15 Fluorocarbons are hydrocarbon derivatives in which *all* hydrogen atoms have been replaced by fluorine, *e.g.*, CF_4 , C_2F_6 , $\text{F}_2\text{C}=\text{CF}_2$, C_7F_{16} . Considerable progress was made in this field during the Second World War, when research was stimulated by the fact that the extreme chemical inertness of these compounds made some of them useful in connection with producing the atomic bomb. Development was aided by the perfection of methods for making hydrogen fluoride relatively cheaply

and in large amounts and by the first commercial production of elementary fluorine.

Free fluorine reacts so violently with hydrocarbons that direct fluorination is impracticable. One alternative method is the replacement of chlorine atoms through the action of HF, as illustrated above in the production of CCl_2F_2 from CCl_4 . But it is not possible to chlorinate the higher alkanes to the stage where all hydrogen atoms have been replaced by chlorine.

A more general method for producing fluorocarbons is to pass the vapors of a hydrocarbon, diluted with nitrogen, over a fluoride such as CoF_3 . In this way it has been possible to obtain, for example, substantial completion of the reaction

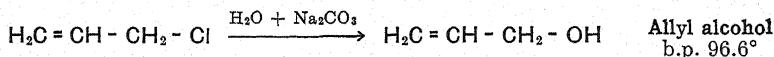


The HF liberated is used to regenerate CoF_3 .

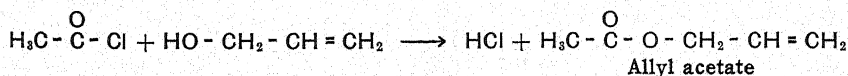
The high indifference of the fluorocarbons toward other chemical substances has been stressed. Their low boiling points—which are close to those of their parent hydrocarbons—and low surface tension point to very slight intermolecular attractions. Practical uses based on these properties are to be expected when fluorocarbons can be produced more cheaply. Lubricants for service under extreme temperature conditions and fire-proofing agents are among the suggested products.

OXYGEN DERIVATIVES OF UNSATURATED HYDROCARBONS

15-16 Allyl alcohol, the best known unsaturated alcohol, is made by the alkaline hydrolysis of allyl chloride:

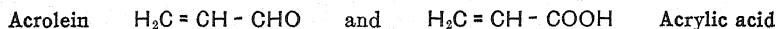


Its chemical properties are quite what would be expected from its similarity to the alkene $\text{H}_2\text{C}=\text{CH}.\text{CH}_3$ and to the primary alcohol $\text{CH}_3.\text{CH}_2-\text{CH}_2.\text{OH}$. Like propene it quickly reduces permanganate and greedily absorbs bromine; under appropriate conditions the double bond likewise adds hydrogen, hydrogen halides, and other chemicals which add to alkenes. Like propanol, allyl alcohol evolves hydrogen when treated with sodium and reacts readily with acyl halides to form esters, *e.g.*,



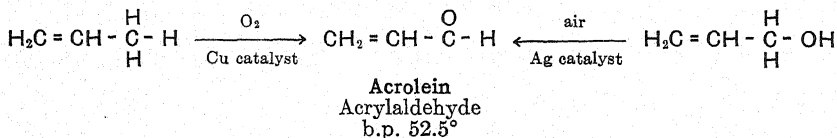
¹ It has been proposed to use the prefix *perfluoro* in naming organic compounds in which *all hydrogen atoms attached to carbon* have been replaced by fluorine; further examples include perfluorobenzene for C_6F_6 and perfluoroacetic acid for $\text{F}_3\text{C}.\text{COOH}$.

Reagents which act on alkenes and also on primary alcohols may affect both functional groups in allyl alcohol or, depending upon conditions, may react predominantly with one or the other. For example, when allyl alcohol is distilled with a concentrated solution of hydrobromic acid, exchange of OH for Br is the prevailing reaction and a good yield of allyl bromide can be obtained; with dry hydrogen bromide gas at somewhat elevated temperatures, addition at the double bond predominates. Oxidizing agents may be chosen to act selectively on the two oxidizable groups. The rapid reduction of permanganate is due almost entirely to oxidation at the double bond. Silver oxide and dichromic acid, on the other hand, act prevailingly on the alcohol group and yield



Predictable properties such as these are characteristic of most unsaturated alcohols. The one important exception is found in alcohols which contain the grouping $\text{RHC}=\text{CH}(\text{OH})$, that is, those in which the OH group is attached directly to one of the $\text{C}=\text{C}$ atoms. The unusual properties of these *enols* are considered in Section 20-13.

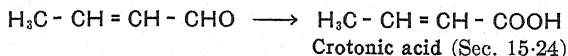
15-17 Unsaturated Aldehydes and Ketones. The simplest unsaturated aldehyde is acrolein. This is produced industrially by the regulated catalytic oxidation of propene and can be made also by oxidizing allyl alcohol:



Acrolein has a very disagreeable, sharp odor which was responsible for its name (L., *acer*, sharp). The vapors are quite toxic and highly inflammable, thus demanding careful precautions in handling.

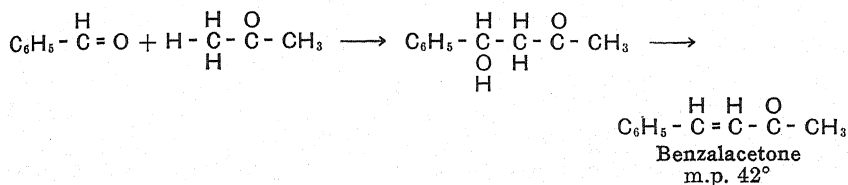
Acrolein contains the ethylenic and the carbonyl double bond and therefore is able to enter into the numerous addition reactions both of the alkenes and of the aldehydes. This makes it a versatile raw material for organic synthesis. The double bonds are conjugated, and each seems to increase somewhat the normal reactivity of the other. The carbonyl group is especially sensitive to oxidation—exposure to air suffices to convert acrolein into acrylic acid. On standing in the absence of air, acrolein polymerizes to a transparent plastic.

Crotonaldehyde is the next higher homologue of acrolein. Its production by the aldol condensation and conversion to butanol have been described (Sec. 10-9). It is readily oxidized to crotonic acid:



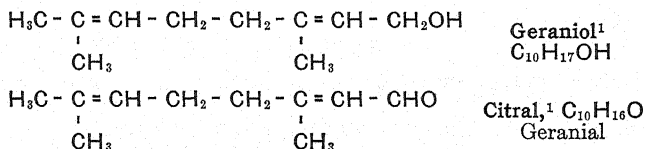
Lacking the $\text{H}_2\text{C}=\text{C}$ group, neither crotonaldehyde nor crotonic acid is easily polymerized.

Other unsaturated aldehydes and unsaturated ketones can be prepared by condensations of the aldol type, *e.g.*,

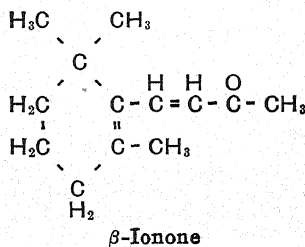
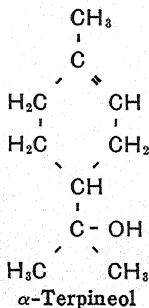


Two molecules of acetone condense similarly to diacetone alcohol, $(\text{CH}_3)_2\text{C}(\text{OH}).\text{CH}_2.\text{CO}.\text{CH}_3$, from which the unsaturated ketone mesityl oxide, $(\text{CH}_3)_2\text{C}=\text{CH}.\text{CO}.\text{CH}_3$, is formed by the elimination of water.

15-18 Terpene Derivatives. Unsaturated oxidation products of the terpenes occur in many essential oils (Sec. 4:11). Some of these, such as oil of citronella and oil of lemon grass, are relatively abundant and cheap and serve as industrial sources of important raw materials for the synthetic-perfumes industry. Among the more abundant components are geraniol and its corresponding aldehyde citral:



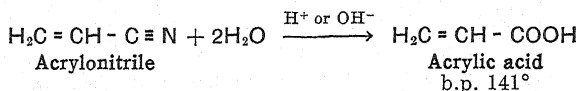
A related synthetic product is the cyclic alcohol terpeneol, which has the odor of lilac. A mixture of α -, β -, and γ -terpineols (isomers which differ in the position of the double bond) is manufactured extensively by chemical reactions from pine oil. Another important synthetic product is a mixture of α - and β -ionone (odor of violets) which is produced by condensing citral with acetone.



¹ Both geraniol and citral occur as mixtures of two isomeric forms which differ with respect to the position of the double bond more remote from the oxygen atom.

Esters of geraniol, terpineol, and other terpene alcohols with acids such as acetic, butyric, and benzoic are also synthesized for use in the perfume industry. β -Ionone is important for this purpose and is also an intermediate in the commercial synthesis of vitamin A (Sec. 4-13).

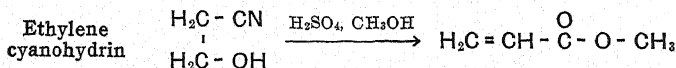
15-19 Unsaturated Acids; Acrylic Polymers. Acrylic acid has long been known as an oxidation product of allyl alcohol and acrolein. It can be made also by hydrolyzing acrylonitrile:



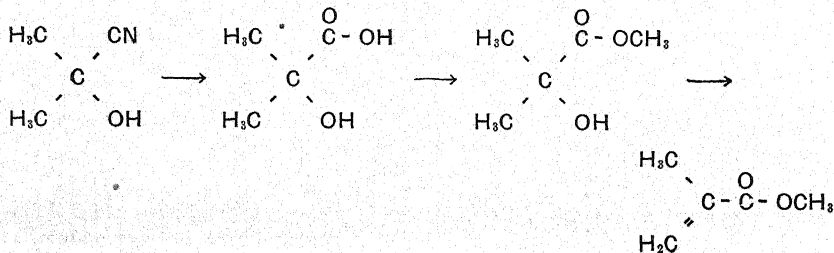
Most of its chemical reactions are those to be expected from the independent reactions of the $\text{C}=\text{C}$ and COOH groups. The exception is the ease with which it passes spontaneously into a transparent, glasslike polymer. This ready polymerization is shared by its esters and also by acrylonitrile, methacrylic acid, and the methacrylate esters.



Acrylic Plastics. Acrylates, methacrylates, and acrylonitrile are produced extensively for polymerization to an important group of thermoplastics. Methyl acrylate is made from ethylene cyanohydrin by heating with sulfuric acid and methanol; in one operation the CN group is hydrolyzed to COOH , the latter is esterified, and water is eliminated to form the $\text{C}=\text{C}$ bond:

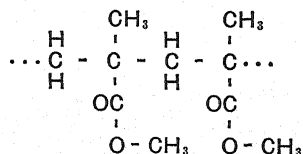


Methyl methacrylate is manufactured in similar fashion from acetone cyanohydrin, obtained by adding hydrogen cyanide to acetone. The intermediate stages may be formulated as follows:



Other esters of both acids are made by using the appropriate alcohols. All polymerize and copolymerize to transparent thermoplastics which differ somewhat from each other in properties such as hardness and softening temperatures.

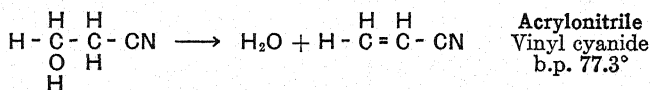
Plexiglas and *Lucite* are trade names of the best known acrylic plastic, which consists principally of polymerized methyl methacrylate:



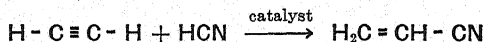
The material takes a high polish, is perfectly clear and colorless, and is highly transparent both to visible and ultraviolet radiation. It is used extensively in the form of cast sheets, which can be readily shaped while hot, for windshields in airplanes. (A soft plastic, it is too easily scratched to be used for this purpose in automobiles.) It is widely used for making transparent ornamental objects. Cast rods, suitably proportioned and bent, will "carry light around a corner."

In order to avoid polymerization during storage and shipment, monomeric methyl methacrylate contains a small amount of an inhibitor—a deoxidant such as hydroquinone. When polymerization is wanted, the inhibitor is destroyed and the reaction catalyzed by adding a little benzoyl peroxide.

15-20 Acrylonitrile is manufactured by dehydrating ethylene cyanohydrin:



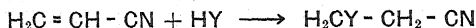
A more recent industrial method is the addition of hydrogen cyanide to acetylene, both of which raw materials are now being produced from natural gas (Sec. 6-13):



The textile fiber Orlon is polymerized acrylonitrile; it is highly resistant to sunlight, mildew, and other destructive agents and also has properties which make it desirable as a wool substitute in clothing. Copolymerization of acrylonitrile with butadiene yields synthetic rubbers of the GR-N type (Hycars, Chemigum, Perbunan) which are not attacked by petroleum hydrocarbons, fats and oils, and most solvents.

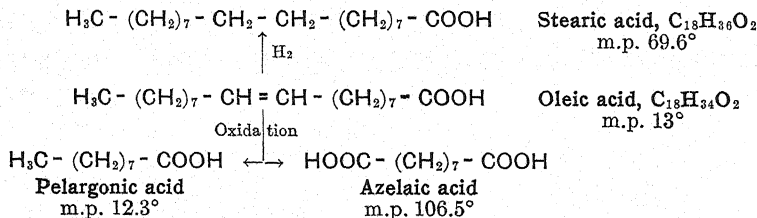
Acrylonitrile is a highly reactive chemical, useful in a wide variety of syntheses. In most of these a compound containing an active hydrogen

atom is added at the $C=C$ bond, spontaneously or with an alkaline catalyst, in the direction indicated by the type equation

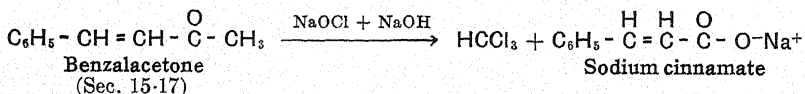


The substances which are thus added include: ammonia and amines; water, alcohols, and phenols; hydrogen sulfide, mercaptans, and thio-phenols; HCl , HBr , and HCN (but *not* carboxylic acids); aldehydes and ketones which have at least one hydrogen atom on the α carbon; and dienes (Diels-Alder reaction, Sec. 19-6). The CN group in these addition products can be hydrolyzed to carboxyl.

15-21 Oleic acid, $C_{17}H_{33}.COOH$, is the most abundant unsaturated acid in nature. It occurs in large quantities esterified with glycerol in the natural fats and fatty acids; its salt, sodium oleate, is a major component of most soap. In its solubility relations and other physical properties oleic acid rather closely resembles hydrocarbons of about the same molecular weight. The presence of a double bond is shown by its ability to reduce permanganate and to add two atoms of bromine. Catalytic addition of hydrogen converts oleic into stearic acid, thus establishing that it has the same, normal, chain structure. The *position* of the double bond—in the middle of the 18-carbon chain—was determined by oxidizing oleic acid and identifying the two 9-carbon acids which are formed by cleavage at the double bond. These relations are summarized in the following scheme:

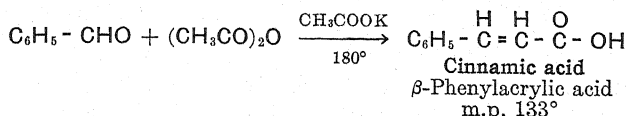


15-22 Cinnamic acid is usually manufactured from benzalacetone by the haloform reaction:



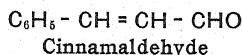
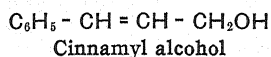
The acid is very sparingly soluble in water and is obtained in shining crystals resembling benzoic acid when the solution of sodium cinnamate is acidified.

Cinnamic acid was first prepared by the prolonged heating of a mixture of benzaldehyde, acetic anhydride, and potassium acetate. The over-all equation is



This method for preparing unsaturated acids—which is known as the Perkin synthesis—is also useful with other aldehydes which do not have an α hydrogen atom. Some other mild alkali, such as potassium carbonate, may be used instead of sodium acetate to catalyze the reaction. The mechanism is similar to that of the aldol condensation.

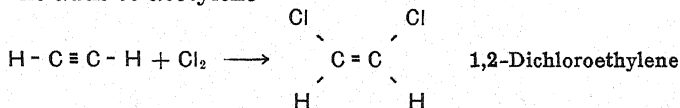
Cinnamic acid occurs in small amounts in certain plants, as do the corresponding alcohol and aldehyde:



Chemical Properties. The ethylenic double bond in cinnamic acid is flanked by two electrophilic groups—phenyl and carboxyl—and adds bromine slowly. Cold permanganate solutions cleave it to give benzaldehyde. This bond is not attacked by the mixed acid used in nitrations, and cinnamic acid yields a mixture of *o*- and *p*-nitrocinnamic acids.¹ The carboxyl group reacts to give the usual types of acid derivatives. Various esters of cinnamic acid and of cinnamyl alcohol are produced for use in the perfumes industry.

GEOMETRICAL ISOMERISM

15-23 Restricted Rotation. The liquid obtained when one molecule of chlorine adds to acetylene



can be fractionated into two isomeric compounds, each with the formula $\text{C}_2\text{H}_2\text{Cl}_2$, boiling at 60.3 and 48.4°C. The chemical relations of these substances show clearly that in both of them one chlorine atom is joined to each carbon, as suggested by the name 1,2-dichloroethylene. (The *position* isomer, $\text{H}_2\text{C} = \text{CCl}_2$, vinylidene chloride, boils at 37°C.) The existence of these two compounds cannot be explained by the principles of isomerism previously considered.

Mechanical models suggest the explanation—see the model for ethylene pictured in Figure 3-1, page 34. The two wire coils connecting the “carbon” balls prevent their rotating about the line between their

¹ It should be noted that the *meta*-directing influence exerted by the COOH group when attached directly to the benzene nucleus is not apparent here, where this group is separated from the nucleus by two carbon atoms.

centers—as is possible when they are joined by a single pin—and all six balls of the model are held *in a plane*. Assume now that one “hydrogen” ball on each “carbon” is replaced by one of another color. This can be done in the two different ways shown in Figure 15·2, where the heavily shaded balls lie on the *same* and on *opposite* sides of the models, respectively.

Let us pass now from mechanical models to the molecules they are intended to represent. When two atoms are joined by a *single* covalent bond, they are able, in general,¹ to rotate freely about the line between

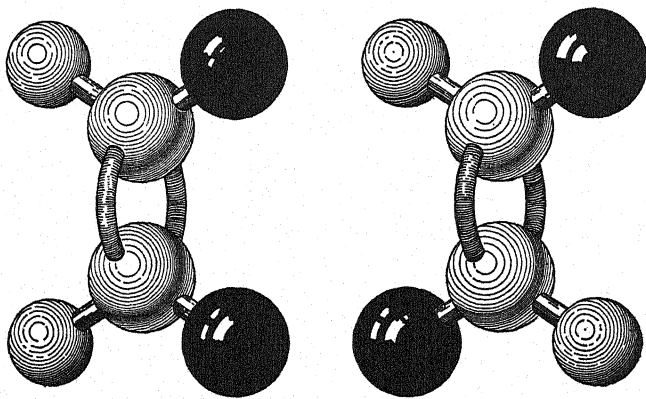
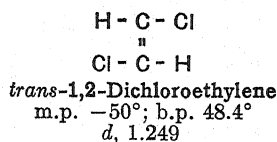
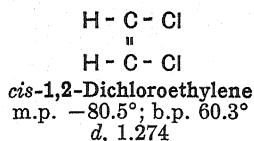


FIG. 15·2 Models representing the *cis* and *trans* forms of geometrical isomers of the type $\text{YHC}=\text{CHY}$, such as 1,2-dichloroethylene.

their centers and isomerism of the kind here in question is not observed, *e.g.*, there is only a single 1,2-dichloroethane. But when two atoms are joined by a *double* bond, mutual repulsions between electrons of the two shared pairs have the effect of the wire coils in the models; the energy necessary to overcome these repulsions is so great that rotation is prevented and the molecule is held in a planar form. Hence, if the shaded balls represent chlorine, Figure 15·2 shows the relative positions of the atoms in the isomeric forms of 1,2-dichloroethylene.

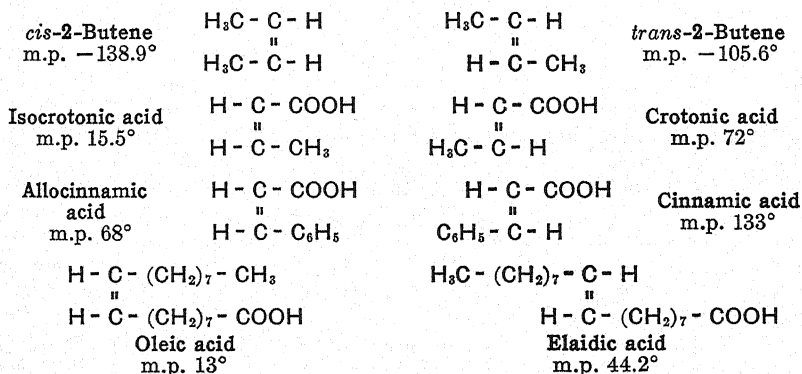
15·24 Cis-Trans Isomers. Compounds related as are the 1,2-dichloroethylenes are called *geometrical* or *cis-trans* isomers. Other typical examples are given below. The relations between any pair can be shown most clearly by writing projection formulas with the $\text{C}=\text{C}$ group vertical and the attached atoms or groups to the right and left, as follows:

¹ Rotation about a single bond is impossible if the atoms joined form part of a closed chain (Sec. 17·17) and may be prevented if certain bulky groups are attached (Sec. 22·17).



The isomer in which like atoms lie on the same side of the molecule is designated by the Latin prefix *cis* (on this side) and the other by the prefix *trans* (across). The structures shown above can be assigned unmistakably from the following additional evidence: The compound boiling at 60.3°C has a dipole moment of 1.89 D, and X-ray diffraction studies give the distance between its chlorine atoms as 3.6 Å; the other has zero dipole moment, and the chlorine distance is 4.1 Å.

It is not always possible to prove so easily which is the *cis* and which the *trans* isomer of other pairs. However, the following observations, which have been found to hold true in a large number of instances, offer a useful guide: The *cis* isomer usually has the lower melting point, the greater solubility, the higher heat of combustion, and (for acids) the higher ionization constant. The melting points of the following pairs are illustrative:



These examples of geometrical isomerism are all drawn from compounds in which revolution is restricted by a carbon-carbon double bond. Examples also occur among compounds containing a $\text{C}=\text{N}$ or $\text{N}=\text{N}$ bond and in certain cyclic molecules (Sec. 17-17).

Questions

1. Explain why there are theoretically possible more derivatives of any higher alkene than of the corresponding alkane, illustrating by the structures of all the possible bromobutanes, $\text{C}_4\text{H}_9\text{Br}$, and bromobutenes, $\text{C}_4\text{H}_7\text{Br}$.

2. If the attempt is made to prepare acetylene in the laboratory by refluxing ethylene dibromide with alcoholic potassium hydroxide, vinyl bromide (b.p. 15.8°C) is the chief product. Explain this fact and suggest experimental conditions under which it should be possible to obtain acetylene by this method.

3. Write structural equations for the reactions to be expected when allyl chloride is treated with: (a) sodium; (b) magnesium and dry ether; (c) benzene and anhydrous aluminum chloride; (d) moist silver oxide; (e) hot alcoholic potassium hydroxide; (f) cold dilute permanganate; (g) bromine; (h) hydrogen bromide; (i) sodium cyanide; (j) ammonia; (k) aniline.

4. Refluxing 1,2-dibromopropane with alcoholic potash yields a mixture of mono-halogen derivatives of propene. (a) Write structural equations showing how three such compounds may be formed and name each of them. (b) In what chemical properties will two of them differ from their isomer, allyl bromide?

5. (a) What general synthetic method is illustrated in the preparation of allyl bromide by heating allyl alcohol with a concentrated solution of hydrobromic acid? (b) What side reaction might be expected to lower the yield of allyl bromide?

6. (a) Give two convenient laboratory tests for distinguishing between allyl bromide and propyl bromide. (b) How could you distinguish between allyl bromide and propargyl bromide, $\text{HC}\equiv\text{C}-\text{CH}_2\text{Br}$?

7. The greater ease of polymerization of vinyl chloride and vinylidene chloride as compared with ethylene shows an influence of halogen atoms on the double bonds in these compounds. What is the most notable effect of the double bond on the halogen atoms?

8. Write a plausible formula for a portion of a copolymer of vinyl chloride with vinyl acetate.

9. The formulas for polymeric vinyl compounds given in Section 15-6 show the *regular* alternation of groups which results if polymerization proceeds consistently by "head-to-tail" additions. Using acrylonitrile as an example, show how addition might occur in such fashion that the CN groups would be scattered irregularly along the carbon chain.

10. Starting with sulfur and coke, show how to prepare: (a) carbon tetrachloride; (b) chloroform; (c) Freon-12.

11. (a) How could you readily distinguish, by a simple physical test, between an *alkyl chloride* and any *dichloro* compound? (b) How would you expect bromoform, CHBr_3 , to differ from chloroform and from iodoform in boiling point and in density? (c) Methylene iodide, CH_2I_2 , is the heaviest known organic liquid (*d*, 3.325). Explain why no heavier liquid can be expected among the halogen derivatives of the hydrocarbons. (d) Using the data in Table 15-2, show how Freon-12 departs from the expected in its boiling point.

12. (a) Explain accurately, in terms of its physical and chemical properties, the use of carbon tetrachloride as a fire extinguisher. (b) Contrast this use of tetrachloromethane with the chief use of the parent hydrocarbon. (c) Calculate the approximate density of gaseous carbon tetrachloride as compared with air at any given temperature. (The average "molecular weight" of air is 28.74.)

13. (a) Explain *why* ethanol is the only primary alcohol, and acetaldehyde the only aldehyde, which responds to the haloform test. (b) Which of the following compounds would give iodoform in the haloform reaction: $\text{C}_6\text{H}_5\cdot\text{CO}\cdot\text{CH}_3$; $(\text{CH}_3)_2\text{CH}\cdot\text{CH}_2\text{OH}$; $\text{C}_6\text{H}_5\cdot\text{CHOH}\cdot\text{CH}_3$. (c) Show how the acid $\text{X}\cdot\text{C}_6\text{H}_4\cdot\text{COOH}$ may be prepared from $\text{C}_6\text{H}_5\cdot\text{X}$ through the successive use of the Friedel-Crafts and haloform reactions.

14. Explain in terms of the electronic theory: (a) the exceptional ease with which a carbon-carbon bond is broken by the action of alkali on chloral hydrate; (b) the exceptional stability of the *ortho*aldehyde structure in chloral hydrate.

15. A student wishing to make the iodoform test on an unknown liquid was unable to find the reagent bottle containing iodine dissolved in potassium iodide solution. Thereupon he used some tincture of iodine from the first-aid cabinet. Criticize the reliability of his conclusions.

16. By the use of general reactions, involving more than one step if necessary and not involving direct substitution of hydrogen by halogen, show how to prepare: (a) 2,3-dibromobutane from 2-butene; (b) 1,4-dibromobutane from 1,3-butadiene; (c) three dibromobutanes from *sec*-butyl alcohol. What raw material would you select, if available, for the preparation of 1,4-dibromobutane?

17. Write structural equations for all the reactions involved in the preparation of the following compounds from $\text{CH}_2\text{Br}.\text{CH}_2\text{Br}$: (a) ethylene diamine; (b) ethylene glycol diacetate; (c) succinic acid; (d) 1,2-diphenylethane.

18. (a) Explain the differences in the products expected when compounds of the types of 1,2-dibromobutane and 1,4-dibromobutane are heated with metallic sodium or zinc. (b) Trimethylene bromide (1,3-dibromopropane) can be obtained by the action of bromine on cyclopropane; write the structural equation and explain. Is it possible to prepare in like manner 1,5-dibromopentane from cyclopentane? Explain.

19. Compare the properties and uses of compounds in which two halogen atoms are attached to the same carbon atom with those of compounds in which they are attached to different ones.

20. From its structural relations to *n*-propyl alcohol and to propene, write equations for the reaction or reactions to be expected when allyl alcohol is treated with: (a) sodium; (b) hydrogen bromide solution; (c) phosphorus triiodide; (d) bromine; (e) nascent hydrogen; (f) cold, dilute permanganate; (g) hot dichromic acid; (h) sodium, followed by ethyl bromide; (i) benzoyl chloride.

21. Show that the reaction of butyraldehyde with polyvinyl alcohol is analogous to the formation of simple acetals (Sec. 10-7).

22. Write equations for the series of reactions through which butanol is manufactured from acetylene, via crotonaldehyde.

23. (a) State how and explain why crotonic acid and oleic acid differ from the acids of the $\text{C}_n\text{H}_{2n}\text{O}_2$ series in their behavior toward oxidizing agents. (b) State and give evidence for the structural relationship between oleic and stearic acids. (c) Explain how the position of the double bond in oleic acid was located. (d) Suggest the basis of a quantitative method for determining the percentage of oleic acid in a mixture of oleic, palmitic, and stearic acids (see Sec. 16-27).

24. Account for the fact that oleic acid, unlike cinnamic acid, adds bromine at about the same rate as its corresponding hydrocarbon.

25. Assuming that *o*-toluic aldehyde and butyric anhydride undergo a Perkin condensation in the presence of a mild alkali, give the successive steps involved and the structural formula of the unsaturated acid to be expected.

26. Give two examples of each of the following general methods for obtaining derivatives of unsaturated hydrocarbons: (a) formation of the ethylenic double bond in a compound already containing the other atom or group; (b) introduction of the other atom or group into a compound already containing the double bond.

27. Explain why the measured dipole moments and chlorine-chlorine distances in the 1,2-dichloroethylenes distinguish between the *cis* and the *trans* isomers.

28. Write projection formulas (following the pattern illustrated in Section 15-24) for the *cis* and *trans* forms of each of the following compounds which may be expected to exhibit geometrical isomerism: (a) 1-butene; (b) *o*-hydroxycinnamic acid; (c) methyl methacrylate; (d) $\text{H}_3\text{C}.\text{CH}=\text{C}(\text{CH}_3).\text{COOH}$.

29. Considering the examples in the last question and those given in Section 15-24, formulate a general rule limiting the possibility of *cis-trans* isomerism in ethylenic compounds.

30. The compounds $\text{C}_6\text{H}_5.\text{N}=\text{N}.\text{C}_6\text{H}_5$ and $\text{C}_6\text{H}_5.\text{CH}=\text{N}-\text{OH}$ both exist in geometrically isomeric forms. Draw projection formulas which explain this fact.

CHAPTER 16

POLYHYDRIC ALCOHOLS AND THEIR DERIVATIVES

16-1 Alcohols that contain more than one hydroxyl group are described as *polyhydric* (dihydric, trihydric, etc.). The *dihydric* alcohols are also known as *glycols*, after ethylene glycol, the simplest compound of this class. No polyhydric alcohol contains more than one hydroxyl group attached to the same carbon atom. All the better known compounds are derivatives of *normal* hydrocarbons.

Boiling points and densities increase somewhat regularly with the number of hydroxyl groups in the molecule, as may be seen from the following examples:

Compound	Formula	Boiling point, °C	<i>d</i>
Propane.....	CH ₃ .CH ₂ .CH ₃	-42.1	0.582 ^{-42°} / _{4°}
<i>n</i> -Propyl alcohol (propanol)....	CH ₃ .CH ₂ .CH ₂ OH	97.8	0.804
Propylene glycol (1,2-propanediol).....	CH ₃ .CH(OH).CH ₂ (OH)	189	1.040
Glycerol (1,2,3-propane-tri-ol)...	CH ₂ (OH).CH(OH).CH ₂ (OH)	290d	1.260

The simpler polyhydric alcohols are viscous liquids, while those containing four or more hydroxyl groups are crystalline solids. Sweetness likewise increases with the number of hydroxyl groups, while solubility in ether, chloroform, and hydrocarbons decreases. All are freely soluble in water.

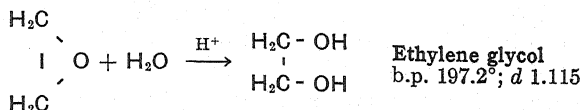
The two polyhydric alcohols of outstanding interest are ethylene glycol and glycerol. These and some of their derivatives will be described in some detail.

16-2 Ethylene glycol was first prepared by Adolph Wurtz (1856), who called it *glycol* (Gr., *glykeros*) on account of its sweet taste. It is a somewhat viscous liquid which is miscible with water in all proportions but less soluble than ethyl alcohol in hydrocarbons and similar organic solvents.

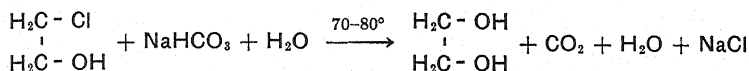
Ethylene glycol is manufactured in large quantities¹ by hydrolyzing

¹ Production in the United States in 1950 was over 500 million pounds.

ethylene oxide with superheated steam and a little acid:



and from ethylene chlorohydrin, as follows:

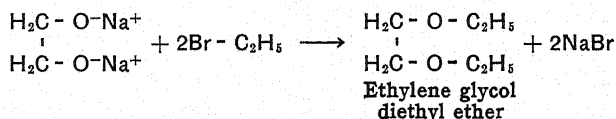


Both ethylene oxide and ethylene chlorohydrin are produced from ethylene.

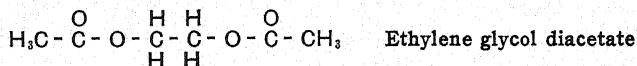
The largest use of ethylene glycol, by far, is as a radiator antifreeze (under trade names such as Prestone). Its value for this purpose depends upon its low volatility at engine temperatures, complete miscibility with water, relatively low molecular weight, and lack of corrosive action. Miscellaneous uses include the manufacture of its dinitrate (mining explosives) and the polyester Dacron (synthetic textile fiber).

16.3 Chemical Properties. Most of the chemical properties of ethylene glycol are those to be expected of a compound containing *two* primary alcohol groups. In other words, ethylene glycol is capable of doing either once or twice whatever ethyl alcohol will do once. The following illustrate the types of products obtainable when both hydroxyl groups react:

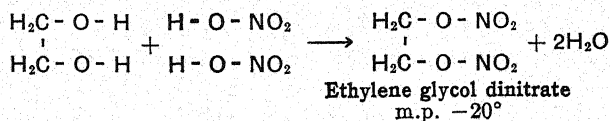
Dialkyl ethers can be prepared by the Williamson synthesis; ethylene glycol is treated with two equivalents of sodium and the disodium derivative heated with an alkyl halide:



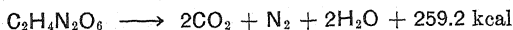
Diacid Esters. Acid anhydrides and acid halides readily esterify both hydroxyl groups; *e.g.*, acetic anhydride yields



The dinitrate is manufactured by the action of cold mixed acid:



When detonated, ethylene glycol dinitrate decomposes explosively in the sense of the equation:



It is used to replace nitroglycerin, wholly or in part, in manufacturing the "short-flame" explosives required for safety in coal mining.

Derivatives of ethylene glycol in which a *single* hydroxyl group has been changed are nearly always prepared from ethylene oxide (Sec. 16·5).

16·4 Oxidation. Just as ethyl alcohol is oxidized successively to acetaldehyde and acetic acid, both primary alcohol groups in ethylene glycol can be oxidized to carbonyl and then to carboxyl. Assuming that each of these changes can occur independently, five different oxidation products may be predicted, as indicated in Figure 16·1. By using the

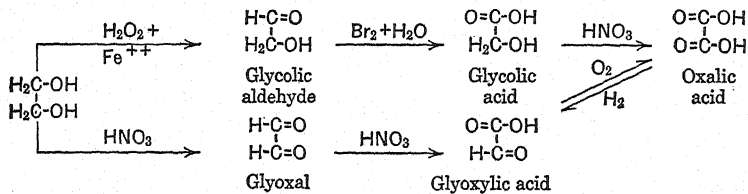


Fig. 16·1 Oxidation products of ethylene glycol (a typical diprimary alcohol).

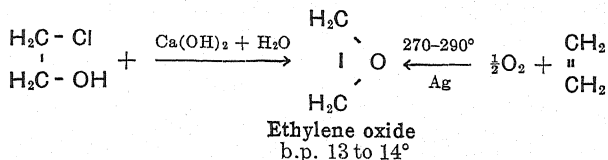
reagents shown, with careful regulation of temperatures, appreciable amounts of each of these have been isolated. A good yield of any one of them except oxalic acid is seldom possible because of the ease with which further oxidation occurs.

The *formation* of glycols at an early stage in the oxidation of alkenes has been mentioned (Sec. 3·14). The further reactions suggested by Figure 16·1 explain why glycols are seldom obtained in appreciable amounts through the action of permanganate or most other oxidizing agents. The important exceptions are concentrated solutions of hydrogen peroxide (30 to 90 per cent) and organic peracids such as peracetic acid (Sec. 11·16). These often give excellent yields of glycols by addition of OH at both sides of the C=C bond. Under somewhat different conditions they may add an oxygen atom *across* the double bond, yielding cyclic ethers with three-membered rings analogous to ethylene oxide. These ethers (epoxides) are readily hydrolyzed to glycols.

Glyoxal is manufactured by the catalytic oxidation of ethylene glycol. It is highly reactive in all the addition reactions of the aldehydes; it readily polymerizes and forms a dihydrate, $(\text{HO})_2\text{HC}.\text{CH}(\text{OH})_2$. Glyoxal is used to decrease the water affinity of polyhydroxy compounds, (*e.g.*, polyvinyl alcohol, starch, and cellulosic materials), by combining with OH groups. It is used in shrink-proofing rayon. Glyoxal is interesting also as the simplest *colored* organic compound (yellow crystals).

Glyoxylic acid always crystallizes as a monohydrate. The water molecule is probably combined with the C=O group as in chloral hydrate.

16.5 Ethylene oxide is manufactured by heating ethylene chlorohydrin with an alkaline solution and by the catalytic oxidation of ethylene with oxygen:

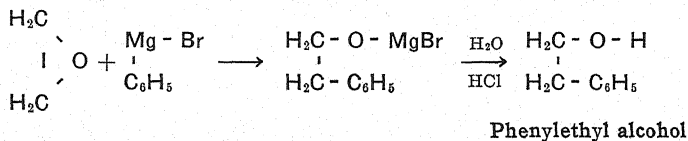


The largest use of ethylene oxide is hydrolysis to ethylene glycol, but it is used also in making many derivatives of the latter as described below.

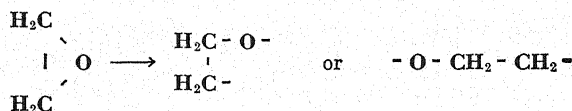
Addition Reactions. Ethylene oxide, a cyclic ether, is much more reactive than the ordinary ethers because of the strain in its three-membered ring (cf. cyclopropane, Sec. 4.4). It reacts readily by ring cleavage and addition with a wide variety of substances including water, hydrogen, acids, alcohols, ammonia, amines, and Grignard reagents. Thus the following products are obtained by addition of:

Water	H - O - CH ₂ - CH ₂ - OH
Hydrogen	H - O - CH ₂ - CH ₂ - H
Halogen acid	H - O - CH ₂ - CH ₂ - Br
Hydrocyanic acid	H - O - CH ₂ - CH ₂ - CN
Ethyl alcohol	H - O - CH ₂ - CH ₂ - O - C ₂ H ₅
Acetic acid	H - O - CH ₂ - CH ₂ - O - CO - CH ₃

Grignard reagents add to form products which are hydrolyzed to higher alcohols. This is a general method¹ for lengthening a carbon chain by two atoms, *e.g.*,

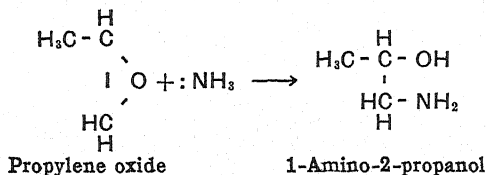


All these reactions may be pictured for convenience as beginning with ring opening in the sense

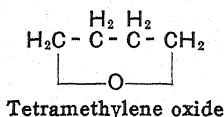
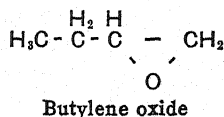


¹ The complications which sometimes arise are considered in more advanced texts.

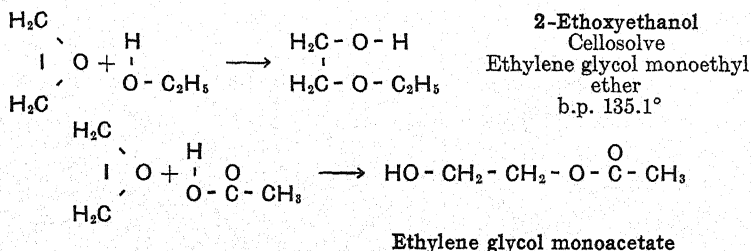
followed by an addition in which a proton (or MgX) adds to the oxygen atom. They are described more accurately as proceeding through nucleophilic attacks on carbon, as in the closely related additions to carbonyl groups (Sec. 10-4). With unsymmetrical compounds such as propylene oxide this attack occurs prevailing at the *least substituted* carbon atom, which is the one expected to carry the higher $+\delta$ charge, *e.g.*,



The high reactivity just described is shared by other cyclic ethers containing *three-membered* rings, *e.g.*, propylene and butylene oxides. Cyclic ethers with strainless rings such as dioxane and tetramethylene oxide are little more reactive than ethyl ether.



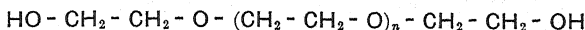
16-6 The addition reactions of ethylene oxide afford the most practical means to obtain many mixed compounds which, from their formulas, *appear* to have been formed from ethylene glycol through reaction at one only of its OH groups. These include ethylene cyanohydrin, $\text{HO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CN}$ (route to acrylonitrile, Sec. 15-20) and many alcohol-ethers and alcohol-acids, *e.g.*,



Some of the monoalkyl ethers (Cellosolves) made in this way are important industrial solvents. This solvent action resembles that of ethanol-ether mixtures, but the higher boiling points of the glycol derivatives render them much more useful, especially in brush lacquers.

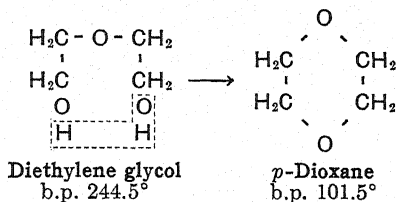
Polyethylene Glycols; p-Dioxane. Ethylene oxide adds ethylene glycol to form the ether-alcohol diethylene glycol, $\text{HOCH}_2\cdot\text{CH}_2\cdot\text{O}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{OH}$

(β,β' -dihydroxyethyl ether). This in turn can combine with another molecule of ethylene oxide to form triethylene glycol. Continuation of the same reaction leads to polyethylene glycols of the general structure



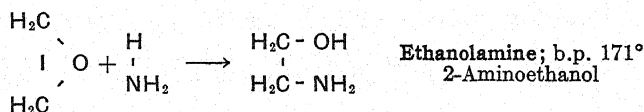
where n may have an average value as high as 140 in certain of the solid polymers (Carbowaxes). Polyethylene glycols have the unusual property of being freely soluble both in water and in aromatic hydrocarbons.

Catalytic dehydration of diethylene glycol yields the cyclic ether *p*-dioxane:

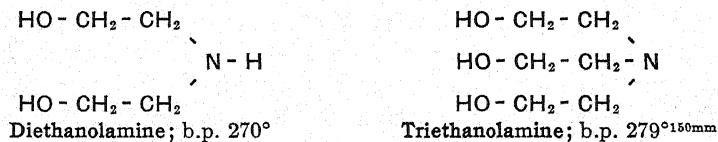


p-Dioxane is a chemically inert ether which is freely miscible with water and with many organic compounds. It is a useful solvent in industry and in scientific research.

16.7 Amino Alcohols. The initial reaction between ethylene oxide and aqueous ammonia proceeds as follows:



The product reacts with excess of ethylene oxide to form diethanolamine and this in turn gives triethanolamine:

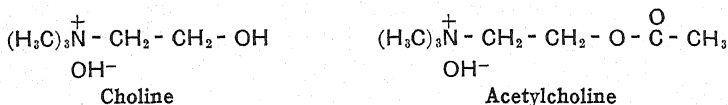


A mixture of these is manufactured from ethylene oxide by reaction with ammonia and is separated by fractional distillation.

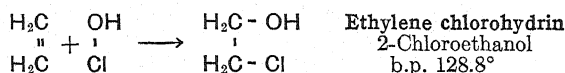
Ethylene oxide reacts in like manner with amines to give amino alcohols such as 2-diethylaminoethanol, $\text{HO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{N}(\text{C}_2\text{H}_5)_2$. This and the related methyl and butyl compounds are useful intermediates in the manufacture of various medicinal products such as procaine and related local anesthetics (Sec. 26.16) and the "antihistamine" Benadryl, the hydrochloride of the base $(\text{C}_6\text{H}_5)_2\text{CH} \cdot \text{O} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{N}(\text{CH}_3)_2$.

Amino alcohols are freely soluble in water, and groups such as $-\text{N}(\text{CH}_2\text{CH}_2\text{OH})_2$ are introduced into certain dyes and other compounds to improve water solubility. Through the nitrogen atom they form salts with acids and otherwise act as organic bases. Hydroxyl groups can be esterified as in any simple alcohol.

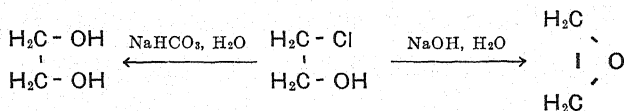
Choline, a quaternary ammonium base related to ethanolamine, is prepared from trimethylamine and ethylene oxide. It is a component of the lecithins (Sec. 16-25) and an important dietary factor included in the vitamin B complex. Acetylcholine is also of biochemical interest because of the part which it appears to play in the transmission of nervous impulses.



16-8 Ethylene chlorohydrin is manufactured by reaction between ethylene and hypochlorous acid¹ under pressure at 20°C:

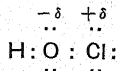


Its major use is for the manufacture of ethylene glycol, either by direct hydrolysis or through intermediate conversion to ethylene oxide:



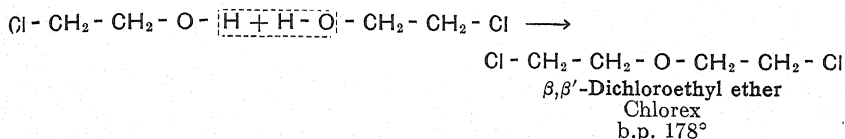
The chlorine atom is displaced easily in the other reactions of the alkyl halides, which makes ethylene chlorohydrin a useful agent for introducing the hydroxyethyl group, $\text{HO}\cdot\text{CH}_2\cdot\text{CH}_2-$, into other compounds. Reaction with sodium cyanide yields ethylene cyanohydrin, thus affording another path (alternate to the reaction of ethylene oxide with HCN) to acrylonitrile and esters of acrylic acid. Ethylene chlorohydrin is freely miscible with water, with which it forms a constant-boiling mixture.

¹ Hypochlorous acid is strongly polarized in the direction



As one consequence, the proton is not easily detached and HOCl is a very weak acid ($K_a = 3.5 \times 10^{-8}$). As a further consequence, HOCl is a ready source of Cl^+ ion; this attacks the $-\delta$ primary carbon atom of the $\text{C}=\text{C}$ bond in an alkene such as propene and HO^- adds to the secondary carbon.

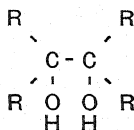
The chloroether Chlorex is a by-product in the manufacture of ethylene chlorohydrin and is also made by heating the latter with sulfuric acid:



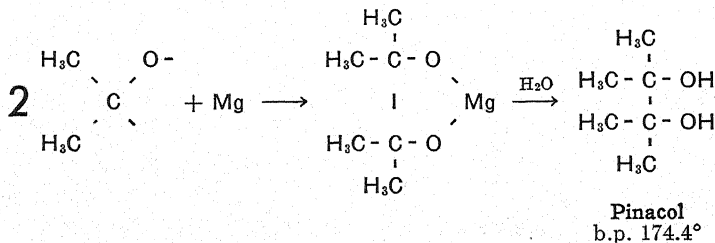
Chlorex is the oxygen analogue of mustard gas (Sec. 14.9) but has no irritant properties. It is a useful industrial solvent, *e.g.*, in refining lubricants.

Halohydrin is the class name for mixed compounds such as ethylene chlorohydrin which are both alkyl halides and alcohols. General methods of preparation are: (1) the addition of HOX to a C=C bond; (2) partial replacement of the OH groups in a polyhydric alcohol through the action of HX.

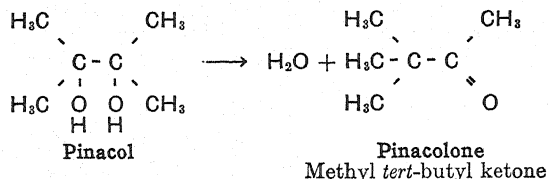
16.9 Pinacols are ditertiary glycols of the type



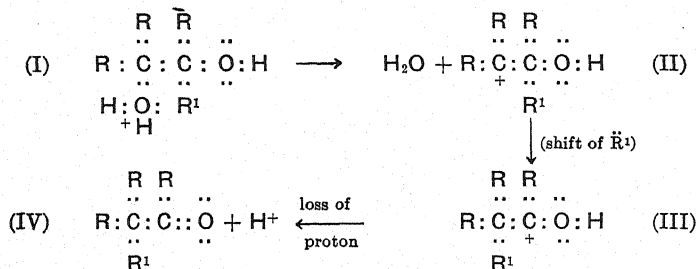
where R may stand for any hydrocarbon radicals, alike or different. (The class name is that of the tetramethyl compound, called *pinacol*.) These glycols are usually formed as by-products when ketones are reduced to their corresponding alcohols and become the main products when certain metal combinations are the reducing agents. Thus when dry acetone dissolved in benzene is treated with amalgamated magnesium it undergoes *bimolecular reduction* to a large extent and good yields of pinacol are obtained when the magnesium compound is decomposed by adding water:



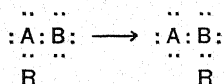
Pinacol-pinacolone Rearrangement. When heated with dilute acids, a pinacol loses a molecule of water and a *hydrocarbon radical migrates* from one tertiary carbon to the other; the products are ketones, called *pinacolones*, containing one quaternary and one secondary carbon atom, *e.g.*,



The mechanism is now generally regarded as that suggested by Whitmore, as follows. Addition of a proton from the catalyst to one of the oxygen atoms gives (I), as with any other alcohol. This weakens the oxygen-carbon bond and permits the elimination of a molecule of water, with formation of the carbonium ion (II). The carbon atom thus left with a +1 charge and an open sextet appropriates an electron pair from its neighbor and *these electrons carry with them* the radical R^1 . The rearranged carbonium ion (III) loses a proton to the solution and yields the pinacolone (IV):



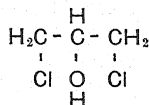
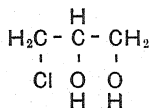
The change of a pinacol into a pinacolone is a *molecular rearrangement* (cf. Hofmann reaction, Sec. 12·15) of the type which has been most studied and about which most is known. This is called a "1,2" shift because it involves migration of a group within a molecule from one atom to an adjacent atom, as indicated by the scheme:



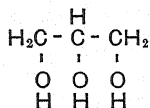
There exist many similar examples in all of which the migration appears to take place within a transitory carbonium ion. Most molecular rearrangements are not reversible and differ in this respect from tautomeric changes (Sec. 20·12).

16·10 Glycerol, commonly called glycerin, is trihydroxypropane. It is obtained principally as a by-product of soapmaking where it is produced by hydrolyzing its esters, the natural fats and fatty oils (Sec. 16·19). A modern synthesis from petroleum, of growing importance, starts with the high-temperature chlorination of propene to allyl chloride (Sec. 15·3). Allyl chloride is readily hydrolyzed to allyl alcohol (with allyl ether as a

by-product) by sodium carbonate solutions. The addition of hypochlorous acid to allyl alcohol and to allyl chloride yields mono- and dichlorohydrins, respectively, *e.g.*,



These are hydrolyzed by alkaline solutions (Na_2CO_3 or NaOH), and the dilute solutions of glycerol thus obtained are concentrated and purified by distillation.



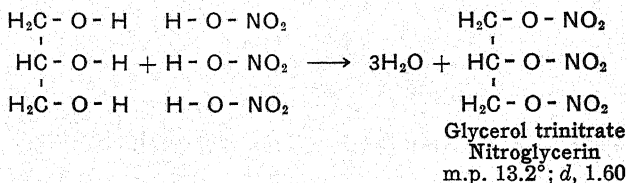
Glycerol
Glycerin
m.p. 17.9° ; b.p. 290° ; d , 1.260

Pure glycerol is somewhat sweeter and more viscous than ethylene glycol. It is completely miscible with and strongly attracts water, absorbing as much as 50 per cent of its own weight when exposed to moist air. It is freely miscible with ethyl alcohol and acetone but is only sparingly soluble in ether and is insoluble in hydrocarbons.

Most of the chemical properties of glycerol are those which would be expected of a compound containing three hydroxyl groups. It reacts with sodium to yield derivatives that can be converted into ethers by the Williamson synthesis. It reacts with acids, anhydrides, and acid halides to form esters (glycerides). Heated with concentrated hydrochloric or hydrobromic acid under suitable conditions, one or two hydroxyl groups can be replaced by halogen to form the corresponding halohydrins.

The annual production of pure glycerol in the United States is of the order of 250 million pounds. Its largest single uses are in manufacturing certain of its esters—especially the alkyd resins (Sec. 24-14) and nitroglycerin. It has innumerable smaller uses in confectionery, tobacco, pharmaceuticals, cosmetics, inks, etc.

16-11 Nitroglycerin (glycerol trinitrate) is manufactured by spraying glycerol on to a well-cooled and vigorously stirred mixture of nitric and sulfuric acids. The reaction proceeds in stages, the first being the formation of mononitrates, but action is continued until all three hydroxyl groups are esterified:



On standing, nitroglycerin separates from the partially spent acid and the latter is gradually displaced by cold water. The ester is separated, washed thoroughly with a solution of sodium carbonate to neutralize all traces of acid, and finally washed with water and dried.

Nitroglycerin is practically insoluble in water but dissolves in alcohol and in many other organic liquids. Like other esters, it is readily hydrolyzed by alkalies (distinction from true nitro compounds). It distills at 160°C under a pressure of 15 mm but when heated under atmospheric pressure explodes at about 260°C. It is also highly sensitive to explosion by shock. It has a powerful effect on living organisms and is used in minute doses medicinally. Precautions against inhaling the vapors, as well as against fire and shock, are necessary when working with it.

A limited amount of nitroglycerin is used, as such, in shooting oil wells; some is used, in conjunction with nitrocellulose, in smokeless powder. Most of the large amount manufactured is converted into dynamite.

16.12 Dynamite. Because it is so sensitive to shock in the liquid form, nitroglycerin is too dangerous to use as an ordinary blasting explosive. This difficulty was overcome by Alfred Nobel, who absorbed it in three times its volume of finely divided siliceous (diatomaceous or infusorial) earth. The explosive thus produced (1867) he called *dynamite*.

In modern practice, Nobel's absorbent has been replaced by wood powder which, by burning, contributes to the volume of gases and the consequent force of the explosion. A considerable quantity of sodium nitrate or ammonium nitrate is also included to aid in burning the wood pulp. The proportions vary with the use for which the explosive is intended; an average dynamite will contain about 40 per cent nitroglycerin, 45 per cent inorganic nitrates, and 15 per cent wood pulp. The well-mixed ingredients are molded into cylinders and enclosed in a paraffined paper wrapper to form the familiar "stick" of dynamite. In the *gelatin dynamites* now widely used the liquid nitroglycerin is colloided to a gel, or plastic mass, with the aid of 2 to 5 per cent of nitrocellulose before being incorporated with the other ingredients.

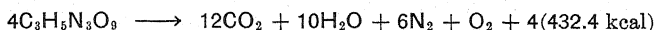
Since pure nitroglycerin solidifies at 13.2°C (about 56°F), dynamite easily freezes in winter; this is dangerous because, on thawing, nitroglycerin is apt to separate. The difficulty is largely overcome by including in dynamite some high-boiling organic liquid which dissolves in the nitroglycerin and thus lowers its melting point. Glycol dinitrate is well suited for this purpose. The latter is also used to *replace* nitroglycerin, wholly or in part, in the "short-flame" explosives required for safety in mining.

Alfred Nobel. Nitroglycerin, discovered by Sobrero in 1847, is said to have remained for nearly twenty years "just an extremely dangerous laboratory curiosity."

Alfred Nobel (1833–1896), a Swedish chemist, recognized its possibilities as an industrial explosive and set about utilizing it. After many accidents—including the loss of one entire factory—he succeeded by making dynamite. Nobel was also the first to make blasting gelatin and nitrocellulose explosives. He left a large part of the fortune which accrued from his manufacture of explosives to establishing the Nobel prizes for outstanding work in chemistry, physics, literature, and the *promotion of peace*.

16-13 Explosives are liquids or solids which, when detonated, decompose rapidly into gaseous products. The force developed increases with the number of molecules of gas, the temperature produced by the heat evolved, and the speed of the reaction. *Rapidity of decomposition*, rather than total energy liberated, is the essential feature of an explosive. Gram for gram, the combustion of cane sugar liberates twice as many calories as the explosion of nitroglycerin.

The complete decomposition of nitroglycerin is represented by the ideal equation



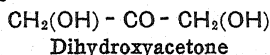
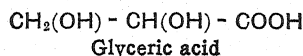
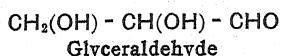
from which it appears that 4 moles produce 29 moles of gas. At the moment of liberation, these are confined within the small space wherein the explosive was packed and are heated to a very high temperature. Hence, they tend to expand and thus reduce the enormous pressure developed.¹ The result is an *explosion*.

"High" Explosives. Nitroglycerin, dynamite, and the military explosives RDX, TNT, PETN, and ammonium picrate all belong to the class known as *high explosives*, or *brisants*. They have detonation velocities of the order of 6500 to 8500 meters per second (the value for black powder is 400) which means that maximum pressure is developed almost instantaneously. Hence the intense *shock wave* which breaks surrounding drilled rock in blasting and shatters buildings in a bombed area. This same property prohibits the use of a high explosive as a *propellant*. The function of the latter is to build up pressure somewhat gradually behind a resting projectile (a bullet, or shell) and expel it from a weapon with the necessary muzzle velocity. The most important propellant explosive is nitrocellulose (Sec. 18-22).

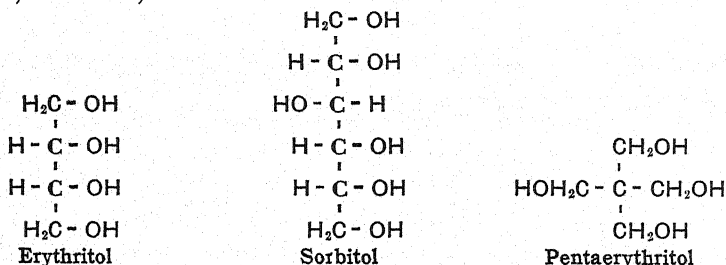
¹ It will be recalled that 1 mole of any perfect gas at 0°C occupies a volume of 22.4 liters when under a pressure of 1 atmosphere and exerts a pressure of 22.4 atmospheres if confined in a volume of 1 liter. Since pressure varies directly with the absolute temperature, it is double at 273°C what it is at 0°C.

Calculations indicate that the explosion of nitroglycerin in a closed space generates a temperature of about 4350° abs; if the explosive occupies 0.12 of the space in which it is confined, the calculated pressure is about 26,000 psi or 1700 atmospheres. Average (40 per cent) dynamite, used under ordinary blasting conditions, develops a temperature of about 1200° abs and a pressure of 9700 psi or 640 atmospheres.

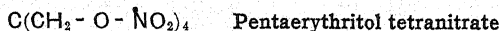
16-14 Oxidation of Glycerol. By the use of a scheme similar to Figure 16-1 it can be predicted that glycerol should yield 11 different oxidation products, excluding any that may arise from cleavage of the carbon chain. Nine of these compounds are known. Some of them occur in nature and others have been made. The following are among those actually obtained by the regulated oxidation of glycerol:



16-15 Higher Polyhydric Alcohols. Plants contain various four-, five-, and six-carbon alcohols with one hydroxyl group attached to each carbon atom. Erythritol and sorbitol are examples. These are all crystalline solids with a sweet taste and are freely soluble in water but practically insoluble in ether and hydrocarbons. They are closely related to the simple sugars and, like the latter, contain asymmetric carbon atoms and exist in stereoisomeric forms (Sec. 18-6). Sorbitol is manufactured by the catalytic hydrogenation of the abundant sugar glucose. It is used in the commercial synthesis of ascorbic acid (vitamin C), in the manufacture of resins, and as a moisture-conditioning agent in tobacco, cosmetics, etc.



Pentaerythritol is a synthetic tetrahydric alcohol manufactured in considerable quantities by condensing acetaldehyde and formaldehyde in the presence of calcium hydroxide (Sec. 10-13). When nitrated with mixed acid each of the four hydroxyl groups is esterified yielding



The product, commonly called PETN, is one of the most powerful high explosives.

Inositols, $\text{C}_6\text{H}_6(\text{OH})_6$, are hexahydric alcohols derived from cyclohexane in which one OH group is attached to each carbon atom. Eight different geometrical isomers are possible (Sec. 17-17). One of these, *meso*-inositol, is widely distributed in plant cells and in various animal organs. A component of the vitamin B complex, it is an essential growth factor

for some strains of yeast and various fungi. Addition to the diet of rats and mice cures skin irritations which develop in its absence. *meso*-Inositol has not been proved essential in human nutrition, but its inclusion in the diet is recommended.

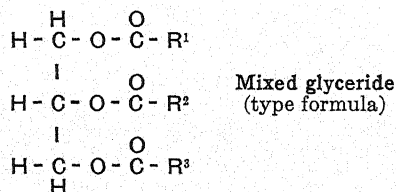
FATS, FATTY OILS, AND RELATED SUBSTANCES

16-16 Fats and fatty oils are plant and animal products of great importance in both their industrial and biochemical relations. In plants, they occur chiefly in seeds; in animals, they are found in deposits consisting almost entirely of fats, such as the leaf lard of hogs, and also interspersed with proteins in the "lean" meat. Those which can be produced in a cleanly manner and free from unpleasant odor or taste are used for human food; others are used mainly for the manufacture of soap and glycerol; a few which, like linseed oil, have the property of "drying" on exposure to air have a special use in paint and varnish. Those which are *liquid at ordinary temperatures* are known, by convention, as *fatty oils*.

Sources. The fats of major industrial importance are milk fat, including cream and butter,¹ and the tissue fats of animals—*lard*, from hogs, *tallow* from sheep, and *suet* from cattle. The most important fatty oils are cottonseed, coconut, soybean, olive, palm, corn, peanut, linseed, and tung. Fish and marine animals also furnish large amounts of oils, especially from their livers.

Animal fats are usually separated from the protein connective tissues by chopping the fatty portions and heating with water or steam (*rendering*). The fat melts and, being lighter than water and insoluble in it, rises to the top of the kettle and is skimmed or drawn off. For the extraction of vegetable oils, the seed or meats are usually ground, cooked, and pressed. The better grades are obtained by cold pressing, after which more oil of somewhat inferior quality is secured by heating and pressing again. The press cake may be broken up and used in feed stuffs, or more oil may be obtained by extracting with a solvent for fats, such as a chlorinated hydrocarbon.

16-17 Structure. *The fats and fatty oils are naturally occurring mixtures of triglycerides, most of which are of the mixed type:*



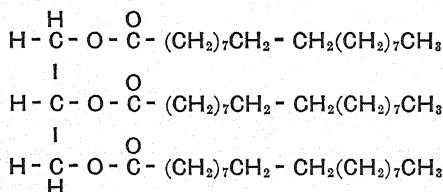
¹ *Oleomargarine* (margarine) is a butter substitute made by churning milk with hydrogenated oils (cottonseed, coconut, soybean); sodium chloride, vitamin A, a coloring matter, and an emulsifying agent are incorporated.

In a simple glyceride R^1 , R^2 , and R^3 represent the same radicals; in the mixed glycerides, with which we are principally concerned, at least two of them are different.

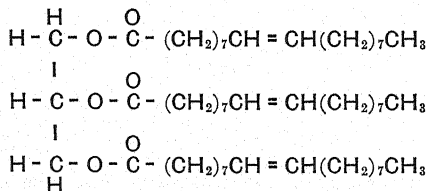
The fat acids¹ esterified with glycerol are monocarboxylic and, with very few exceptions, contain *nonforked* chains with an *even* number of carbon atoms. The most abundant of the saturated acids (Table 11-1) are: *palmitic*, C_{16} ; *stearic*, C_{18} ; *lauric*, C_{12} ; and *myristic*, C_{14} . The unsaturated *oleic* acid (Sec. 15-21) is widely distributed in fatty oils. Individual natural products often show characteristic differences in the acid distribution. Thus the glycerides of milk fat contain significant amounts of butyric and of the C_6 , C_8 , and C_{10} saturated acids. The glycerides of castor oil contain much *ricinoleic* acid (12-hydroxy-9-octadecenoic), one of the few hydroxy acids found in fatty oils. C_{18} acids with three to six double bonds are abundant in fish oils. The highly unsaturated acids of linseed and other drying oils are mentioned in Section 16-24.

All the saturated acids from C_{10} upward are solid at room temperature, while oleic acid (m.p. $13^\circ C$) and other unsaturated acids are liquids. A like relationship holds between the glycerides of saturated and unsaturated acids, *e.g.*,

Stearin
Glycerol tristearate
m.p. 71.5° ; 55.0° †



Olein
Glycerol trioleate
m.p. 4.9° ; -12° †



Thus it appears that *unsaturation* in the acid radicals is the chief factor determining whether a particular glyceride will be a fat or an oil. The *iodine number* (Sec. 16-27) is a quantitative measure of unsaturation.

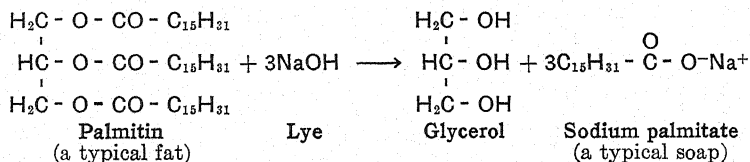
¹ The term *fat acids* refers to all acids, both saturated and unsaturated, which occur in the glycerides of natural fats and fatty oils. Compare with *fatty acid series*, Section 11-1.

† Glycerides, fatty acids, and many other compounds containing long, unforked chains often crystallize in two or more polymorphic forms of different melting points.

16-18 General Properties. The fats and fatty oils are freely soluble in hydrocarbons, chlorinated hydrocarbons, ether, and acetone but are insoluble in water and all water solutions. They form stable emulsions when agitated with water in the presence of a little soap or gelatin. Milk is an emulsion in which droplets of butter fat (averaging 3 to 10 microns in diameter in cow's milk), are dispersed in water; this emulsion is stabilized by an adsorbed protein and phosphatide film. All fats and oils are lighter than water. They are nonvolatile, even with steam and at reduced pressures, for which reason the fatty oils are often called *fixed* oils. This is in distinction from the *mineral* oils (from petroleum) and the *essential* oils (Sec. 4-11), both of which types can be distilled.

When pure, the fats and fatty oils are odorless and practically tasteless. On standing they often develop an objectionable odor and taste and are then described as *rancid*. This appears to be due mainly to the formation of aldehydes by autoxidation at the double bonds of unsaturated glycerides. The development of rancidity in a purified oil is retarded by excluding light, air, and moisture and also by adding small amounts of certain chemicals, such as hydroquinone, that serve as antioxidants.

16-19 Saponification; Soapmaking. Hydrolysis is the most important reaction of the fats and fatty oils, as it is with other esters. Alkaline hydrolysis—saponification¹—is the usual method and the key reaction of the very large “soap and glycerin” industry. Raw materials are those fats and oils which for any reason are not in demand for use as foods. These are carefully sterilized, deodorized, bleached, and usually hydrogenated (Sec. 16-23). Saponification is conducted by heating with steam and sodium hydroxide solution (lye):



When saponification is complete, the soap is “salted out” by saturating the spent lye with sodium chloride. The residual liquor contains about 10 per cent of glycerol with some excess alkali, a large amount of sodium chloride, and various impurities. It is neutralized and then concentrated by vacuum evaporation to about 80 per cent glycerol; during this process most of the sodium chloride crystallizes out. Some of this “crude glycerin” finds uses as such. The remainder is distilled with live steam

¹ The term saponification (from L. *sapo*, soap), which is now applied generally to the alkaline hydrolysis of esters, arose from the fact that this reaction has been used in *soapmaking* since very early times.

in a high vacuum and thus separated from the remaining nonvolatile impurities; after concentration to about 99 per cent glycerol it is sold for the uses described in Section 16-10.

Other methods of hydrolysis (*e.g.*, by steam at 650 psi and 245°C, or with the aid of acid catalysts) yield glycerol and a mixture of free fat acids. The latter may be used as such for making special soaps by reaction with oxides, hydroxides, or carbonates of various metallic elements. In another application of growing importance the individual acids are separated in a state of comparative purity by fractional distillation at very low pressures. The acids can be converted into the corresponding amines through their ammonium salts and nitriles (Sec. 13-8).

Soap. The crude soap salted out after saponification with lye is a mixture of the sodium salts of whatever acids were combined with glycerol in the soap stock—for the most part, sodium oleate, palmitate, and stearate. It is washed to remove excess alkali, is partially dried, possibly colored and perfumed, and pressed into cakes or converted into flakes, chips, or powder. Potassium soaps, which are softer and more soluble in water than the sodium salts, are produced in considerable but much smaller quantities by saponification with potassium hydroxide and used in special products such as "soft" soap, liquid soaps, shaving creams, etc.

The above description applies to what the ordinary purchaser gets when he buys "soap" for use as a cleansing agent. In chemistry and technology, however, the term soap is more comprehensive and includes the salts of all long-chain and complex carboxylic acids of 12 or more carbon atoms. Metallic soaps are salts of metals such as lead, cobalt, and copper with the fat acids, resin acids, or naphthenic acids (Sec. 11-11). All these are useless for washing because they are insoluble in water, but they are manufactured for various special uses such as *driers* for paints and printing inks, emulsifying agents in greases, and as fungicides, etc. Purely organic soaps are made by neutralizing fat acids with an organic base such as triethanolamine; these soaps dissolve in hydrocarbons and chlorinated hydrocarbons, a property which makes them useful in dry cleaning.

16-20 Detergency. The principal use of ordinary soap depends on its cleansing or *detergent* action on our skin, clothing, dishes, etc. The explanation of this action involves the role of soap as an emulsifying agent.

Emulsions consist of small drops of one liquid suspended in another liquid, the two being insoluble, or nearly insoluble, in each other. The one which is broken into drops is called the *dispersed* phase and the other, the continuous phase. The droplets are usually several microns in diameter. When two *pure* liquids such as benzene and water are shaken together vigorously, a milky emulsion is formed but is very temporary and soon separates into clear layers of benzene and water. To prepare emulsions which are relatively permanent, it is necessary to have present a small amount of an emulsifying agent such as soap.

Ordinary soap—we may think of it as sodium oleate—is an effective emulsifying agent because the benzene droplets dissolve the long $C_{17}H_{33}$ tails but not the polar COO^- group at one end. The latter remain in the surface-layer in contact with water (and a roughly equivalent number of Na^+ counter ions). This polar surface-layer prevents little drops of benzene from coalescing into big ones; and, because of the attraction between the COO^- groups and water, the surface tension between benzene and water is reduced¹ and either liquid can “bend” more easily about droplets of the other. Both factors contribute to the stability of an emulsion. Sodium oleate gives benzene-in-water emulsions; with magnesium oleate, water can be dispersed in benzene, or in an oil.

Detergency involves the same principle. The “dirt” on the hands or clothing is held there by oil or grease. This is emulsified by rubbing with soapy water. Rubbing is an essential part of successful washing because it exposes fresh layers of the grease. Each layer is coated, as formed, with an adsorbed layer of soap molecules—hydrocarbon tails dissolved, polar groups on the outside in contact with water. The layers cannot stick together again—as they do when a greasy surface is rubbed with plain water—and are readily rinsed away.

The sodium salts of the straight chain acids C_{12} to C_{18} , saturated and unsaturated, are satisfactory detergents for general purposes. Above C_{18} , they are too insoluble in water; below C_{12} the hydrocarbon chains are too short. The sodium salts of abietic and other resin acids are also satisfactory, and these are often incorporated into laundry (“yellow”) soaps.

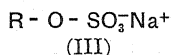
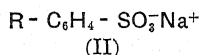
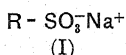
Limitations of Soap. Ordinary soaps are inefficient in hard water and sea water and are useless in acid solutions. Hard water contains Ca^{++} and Mg^{++} ions which combine with the soap anions and precipitate insoluble calcium and magnesium soaps as a scum. This means a waste of soap for, until these cations are removed, it is not possible to get lathering or much detergency. Sea water contains magnesium ions and, in addition, its high sodium ion content serves by common-ion effect to lower the solubility of soap and thus decrease its efficiency. Soaps have no detergent action in acid solutions because the free fat acids are precipitated. This occurs to some extent at any pH lower than about 9.5 to 10.2, which is the value measured when the purest soaps are dissolved

¹ The surface tension of pure water against air is 72 dynes per square centimeter at 25°C; this value drops to 25 to 30 dynes in a soap solution. Similarly, soaps at a concentration of 0.2 per cent reduce the interfacial tension between water and oil to the order of 5 dynes. A simple demonstration consists in placing a drop of water and a drop of soap solution on a piece of oiled paper or a block of paraffin. The water “stands up” in a form approaching a sphere; that is, the area of contact is as small as gravity will permit. The soap solution, on the contrary, spreads out over the oily surface and “wets” it.

in distilled water. So-called "built" soaps contain salts such as sodium phosphates or silicates, which neutralize any acidity derived from the objects washed and thus protect the soap. Most soaps also contain sodium chloride or sodium sulfate, which improve their colloidal properties in solution.

16-21 Synthetic Detergents. The limitations in the uses of ordinary or "natural" soap have led to the large-scale manufacture of synthetic detergents and other surface-active agents.¹ All these follow the pattern of the natural soaps in that they contain a long-chain, nonpolar hydrocarbon radical—soluble in oil but insoluble in water—in combination with a polar group which attracts water and dissolves in it. These essential parts of surface-active compounds are called *hydrophobic* and *hydrophilic*, respectively (cf. footnote 1, page 40).

The three types of synthetic detergents made and used most extensively² are compounds which can be represented by the type formulas



(Their production, as described in Sections 14-6 and 14-7, should be reviewed.) The hydrophobic part of each, R, is a C₁₂ to C₁₈ hydrocarbon residue. The hydrophilic part is the ionized, highly polar sulfonate (I and II) or sulfate group (III). Since the surface-active agent in these compounds—and in the natural soaps—is a negative ion, they are described as *anion-active* or *anionic* detergents.

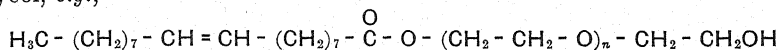
Cationic detergents have been called "invert" soaps because the active component is a *positive* ion. Most of them are acetates or other simple salts of long-chain alkyl amines, such as octadecyl ammonium chloride, C₁₈H₃₇NH₃⁺Cl⁻. Or these amines may be converted into quaternary ammonium salts (Sec. 13-5), which furnish cations of the type R₄N⁺. The required long-chain amines are made from the fat acids. These cation-active compounds are powerful detergents but relatively quite

¹ All "surface-active" agents have in common the property of reducing interfacial tensions. In addition to detergents, they include wetting, foaming, penetrating, dispersing, and emulsifying agents. A given substance may be useful for several of these purposes but is usually superior in some one of them. For example, certain "wetting agents" are far better than soap in preparing textiles for dyeing but not as good detergents.

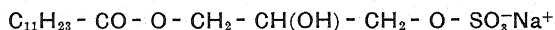
² An allied type which is also produced in considerable quantities is made by the action of sulfuric acid on certain oils, fats, and waxes. Addition of sulfuric acid at C=C bonds yields products of the type R.O.SO₃H, which are converted into sodium salts. Castor oil has long been used for this purpose because the OH group of its ricinoleic acid molecules is easily esterified by sulfuric acid. The products here described are commonly but incorrectly called *sulfonated* oils, fats, etc.; the correct term is *sulfated*.

expensive and have found their major uses for purposes not directly related to this property. They are highly bactericidal and are used as germicides, fungicides, and disinfectants; some of them provide the basis for water-repellant finishes for cloth; and they are useful in firmly fixing direct acid dyes to cellulosic materials.

Nonionic Surface-active Agents. The hydrophilic property of these compounds is supplied by a group containing a considerable number of oxygen atoms capable of hydrogen bonding with water. A favorite type consists of an acid such as stearic or oleic esterified with a polyethylene glycol, *e.g.*,



Highly effective (but rather poorly foaming) detergents are obtained when n has a value around 15. Others include ethers of polyethylene glycol with higher alcohols or with alkylated phenols or naphthols, *e.g.*, the dodecylphenyl ether of hexaethylene glycol. The hydrophilic group can be shortened and foaming improved by sulfating a hydroxyl group (which, of course, converts the product to the anionic type). Vel, a typical example, is produced by heating coconut oil with excess glycerol to obtain monoglycerides (by transesterification) and sulfating:



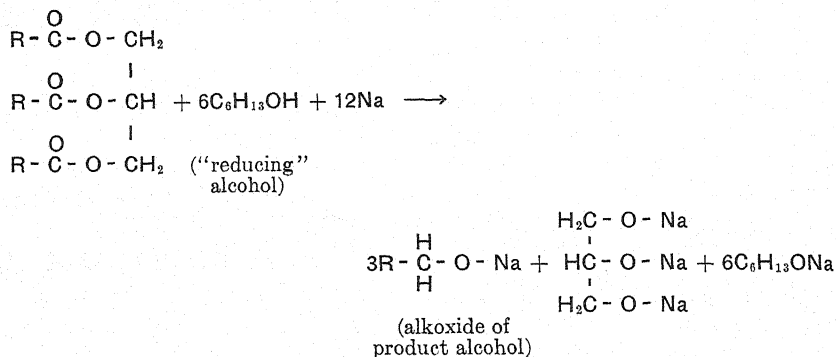
Oil-soluble nonionics such as glycerol monostearate are important emulsifying agents in oleomargarine, cooking fats, cosmetics, lubricating greases, etc. Monoesters of other polyhydric alcohols, such as pentaerythritol, sorbitol, diethylene glycol, etc., are used similarly.

Production. The manufacture of surface-active agents has been expanding steadily and rapidly since the Second World War. Current annual production (1951) in the United States is estimated at 1.5 billion pounds of industrial products. This is somewhat more than half the weight of natural soaps manufactured.

The popularity of synthetic detergents rests largely upon their effectiveness in hard water and over a wide pH range. Their major disadvantage for personal use is that they may be too good—that is, remove too much of the natural oil from the skin or hair.

16-22 Reduction of Fatty Oils. The long-chain alcohols required for making the alkyl sulfate detergents, $\text{R.O.SO}_3^- \text{Na}^+$, are obtained by reducing fatty oils. This can be done by high-pressure catalytic hydrogenation at elevated temperatures, but the process is expensive and unsatisfactory in that it saturates double bonds. A more effective industrial practice is a modification of the Bouveault-Blanc reaction (Sec. 12-8). A carefully dried oil, preferably coconut oil, mixed with an

alcohol such as 2-hexanol and dissolved in toluene, is treated with metallic sodium emulsified in toluene. A typical reduction is indicated by the equation



In effect, the hydrogen atoms liberated by the action of sodium on the "reducing alcohol," 2-hexanol, reduce the fatty-acid residues to their corresponding alcohols (actually, alkoxides).

The reaction mixture is dropped into water, which hydrolyzes the alkoxides to alcohols and sodium hydroxide. Toluene, 2-hexanol, and the product alcohol $\text{R.CH}_2\text{OH}$ form a floating oily layer which is drawn off and distilled. Fractionation separates the product alcohol from the reducing alcohol and toluene, which are returned to the operation. The water layer, containing sodium hydroxide and glycerol, can be used for saponification in an affiliated plant producing natural soaps.

The mixture of alcohols obtained by reducing a typical coconut oil consists of about 50 per cent lauryl alcohol, $\text{C}_{12}\text{H}_{25}\text{OH}$, and 35 per cent of C_{14} , C_{16} , and C_{18} alcohols.

16-23 Hardening of Oils. Reference to the formulas in Section 16-17 shows that olein (m.p. 4.9°C) differs structurally from stearin (m.p. 71.5°C) only in the three double bonds in its molecule. Saturation of these bonds by catalytic addition of hydrogen converts the former into the latter. This is the principle of the process known as the *hardening of oils*, which is used industrially on a very large scale for converting vegetable oils into higher melting products.

The method is a modification of the Sabatier reaction, which cannot be used in its original vapor-phase form because fatty oils are nonvolatile. The essential requirement is to bring into *intimate* contact at 175 to 200°C a fine spray of oil, hydrogen at about 150 psi, and an active catalyst such as Raney nickel. By varying the length of treatment and other operating factors it is possible to hydrogenate to complete saturation or to stop at some intermediate stage which gives a product with the consistency desired. Hardening of oils reduces the tendency to become rancid and has other advantages in the manufacture of food products. It is used

also on certain oils intended as soap stock because they yield better soaps after partial hydrogenation.

Inhabitants of the temperate zones have long been accustomed to cooking with *semisolid* fats (lard and butter) and demand that property in any substitute. For this reason the hardening of oils such as cottonseed has become a very large-scale industrial procedure for manufacturing cooking fats which are sold under many trade names (*e.g.*, Crisco). Complete hydrogenation gives fats with melting points too high for general use; these may be blended with untreated oil to make a product of the consistency of lard, *i.e.*, melting at about 40 to 45°C.

16.24 Drying Oils. When exposed in thin layers to air, certain fatty oils absorb oxygen, with gain in weight up to 30 per cent, and are converted into tough elastic films of *linoxylin*. This change, which is familiar in the use of paints, is called *drying*. Linseed, perilla, and tung oils possess the drying property in higher degree than any others widely available and for this reason have a special and extensive use in paints, varnishes, printing inks, linoleum manufacture, etc. They owe this property to their high content of glycerides of acids containing two or three double bonds. The most abundant of these contain 18-carbon chains with double bonds in the positions indicated: linoleic acid, 9, 12; linolenic acid, 9, 12, 15; eleostearic acid, 9, 11, 13.

In the initial stage of drying, oxygen is taken up at double bonds to form peroxides:



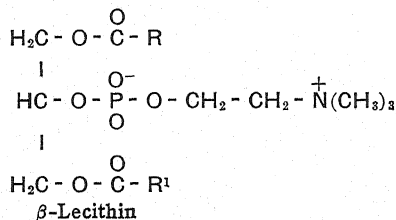
The further steps are complex and remain obscure; peroxides reach a maximum and then disappear in a polymerization which produces the semisolid *linoxylin* film.

Driers are substances added in small amounts to catalyze the addition of oxygen and thus shorten the drying time of paints, printing ink, etc. The most effective are oil-soluble metallic soaps (*e.g.*, lead, manganese, cobalt, increasing in this order) of long-chain fatty acids such as linolenic.

Paint is manufactured by grinding a suitable pigment such as white lead, lead chromate, or ferric oxide (or a color lake, Sec. 25.24) with linseed oil containing a drier. Turpentine or a petroleum distillate may be added to thin the oil and thus permit a more even coating. During drying the thinner evaporates, but the essential feature is the formation of *linoxylin*. This binds the pigment to the object painted and forms the water-insoluble coating which protects the surface from rust or rotting. *Oil varnishes* contain a drying oil and a natural resin dissolved in a suitable solvent; drying of the oil gives the protective film to which the resin adds gloss. These have been displaced very largely by surface coatings called

lacquers, enamels, etc., which are films of synthetic resins, notably modified alkyds (Sec. 24-14) and pyroxylin (Sec. 18-23). Ordinary *printing ink* is made from carbon black and drying oils well fortified with driers. *Linoleum* is made by mixing ground cork with a drying oil and spreading on a fabric backing.

16-25 Phosphatides¹ are glycerides of the higher carboxylic acids, but on hydrolysis they yield also phosphoric acid and a nitrogenous organic base. The ones best known are the *lecithins*, which are especially abundant in egg yolk and in brain and nervous tissues. In the lecithins two hydroxyl groups of glycerol are combined with long-chain acid radicals, one of which at least is unsaturated. The third hydroxyl is esterified with phosphoric acid, and this, in turn, is united with the quaternary ammonium base *choline* (Sec. 16-7).



The *cephalins* are similar to the lecithins but contain as the base *ethanolamine*, $\text{HO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{NH}_2$, sometimes called *cholamine*. Various other phosphatides are known which contain the complex base *sphingosine*, $\text{C}_{18}\text{H}_{37}\text{O}_2\text{N}$.

The occurrence of phosphatides in the most essential parts of living tissues, such as brain and nerve cells, suggests that they play a very important part in life processes. Their exact mode of functioning is not clear, but it appears, for one thing, that fats are *transported* in the animal body in the form of phosphatides both when they are being deposited and when they are being taken out of the storage depots preparatory to combustion as fuel.

16-26 Waxes are esters of even-numbered long-chain acids, C_{24} to C_{36} , with *monohydric* alcohols of high molecular weight. Some of these alcohols are even-numbered members of the ethanol series from C_{16} to C_{36} ; others are sterols (Sec. 27-18). As they occur in nature, waxes are usually mixtures of several such esters together with certain amounts of uncombined alcohols and hydrocarbons—all of high molecular weight.

¹ The phosphatides are known also as phospholipides. *Lipide* is a collective term for natural compounds of biochemical importance which are insoluble in water but soluble in ether, chloroform, and hydrocarbons. Besides the fats and fatty oils, it includes phosphatides, waxes, and the sterols (Sec. 27-18).

Honeycomb, or *beeswax*, is a familiar example. The wax esters can be saponified but, probably on account of their extreme insolubility, this occurs much less easily than with the fats and fatty oils.

Carnauba wax, obtained from the leaves of the carnauba palm of Brazil, is used extensively in making wax polishes; it consists largely of the triacontyl, $C_{30}H_{61}$, esters of C_{26} and C_{28} acids. *Spermaceti*, a solid obtained from cavities in the head of the sperm whale, is largely cetyl palmitate, $C_{15}H_{31}.CO.O.C_{16}H_{33}$. Sperm oil from the same source is a valuable lubricant for certain special purposes. *Wool wax*, commonly called wool fat, consists largely of esters of cholesterol (Sec. 27·19) and its isomers. It is characterized by the readiness with which it absorbs water and is absorbed by the skin; a purified preparation called *lanolin* is used in pharmacy as a base for ointments.

16-27 Fat-and-Oil Analysis. Industrial controls require the determination of total fat in various products, such as milk and cottonseed, and the use of many physical and chemical tests to establish the identity of oils, the presence of adulterants, etc. Many of these procedures are important also in biochemical research. Most of them are too specialized for description here, but the principles of two widely used chemical analyses should be understood.

Iodine Number. A weighed sample of the fat or oil is treated with a measured volume of a standard solution of iodine chloride or iodine bromide. The well-stoppered container is allowed to stand in the dark for a suitable length of time, after which the remaining free halogen is determined by titration with a standard solution of sodium thiosulfate. The halogen which has disappeared is that which was added at the double bonds and is, therefore, a measure of the degree of unsaturation. This is always calculated and reported in terms of iodine. The *iodine number* is defined as the number of grams of iodine added by 100 grams of the sample. Olein contains three double bonds, one for each oleic acid residue; hence, 1 mole (885 grams) absorbs $3 \times 2 \times 127$ grams of iodine or 86.2 grams of iodine per 100 grams and its iodine number is 86.2. The corresponding value for the highly unsaturated linseed oil approaches 200.

The *saponification number* is determined by refluxing a weighed sample with a measured volume of standard alkali and titrating the excess of alkali remaining when the reaction is complete, as in determining the saponification equivalent of a simple ester (Sec. 12·7). The result is calculated and reported as the number of milligrams of KOH required to saponify 1 gram of the sample.

Questions

1. (a) Why is it to be expected that any polyhydric alcohol will contain at least as many carbon atoms as hydroxyl groups? (b) Summarize the relations between physical properties and the number of hydroxyl groups.

2. (a) Adolph Wurtz originally obtained ethylene glycol by heating ethylene dibromide with silver acetate and hydrolyzing the product; write the equations. (b) Write structural equations for the two present methods for manufacturing ethylene glycol from ethylene.

3. Explain the bearing of each of the following properties of ethylene glycol on its suitability for use as an antifreeze in automobile radiators: (a) high boiling point; (b) low molecular weight; (c) miscibility with water; (d) neutral reaction.

4. Ethylene glycol is formed when ethylene is treated with permanganate solution in the von Baeyer test for unsaturation; explain why no process for the manufacture of ethylene glycol is based on this reaction.

5. Prepare diagrams similar to Figure 16-1 showing all the *three-carbon* products which could arise through the regulated oxidation of: (a) 1,2-propanediol (propylene glycol); (b) 1,3-propanediol (trimethylene glycol).

6. Write equations for the reactions of ethylene oxide with: (a) water; (b) butanol; (c) *n*-butylmagnesium bromide; (d) ammonia; (e) propionic acid; (f) hydrocyanic acid; (g) aniline.

7. (a) With what compound is ethylene oxide isomeric? (b) Describe in detail the similarities that you observe in the chemical reactions of these isomers.

8. The following compounds represent five different types of ethers that may be regarded as derived from ethylene glycol: ethylene oxide, Cellosolve, ethylene glycol diethyl ether, diethylene glycol, and *p*-dioxane. Show by formulas and state in words how each of these is related to ethylene glycol.

9. (a) How would you convert Cellosolve into its ester, Cellosolve acetate? (b) What is the best way to prepare ethylene glycol monoacetate? (c) Given ethylene oxide, ethylene glycol, and ethyl alcohol, outline the best sequence of reactions for making the monoethyl ether of diethylene glycol.

10. Account for the facts that: (a) butyl Cellosolve (mol. wt. 118) has a higher boiling point and is more soluble in water than Cellosolve acetate (mol. wt. 132); (b) *p*-dioxane has a much lower boiling point than diethylene glycol although there is little difference in molecular weight.

11. Account for: (a) the properties of triethanolamine as a base; (b) the higher boiling point and water solubility of ethylene chlorohydrin in comparison with ethylene dichloride; (c) the direction of addition of hypochlorous acid to propene; (d) the fact that tetramethylene oxide lacks the high chemical reactivity of ethylene oxide.

12. (a) Write full structural equations for the bimolecular reduction of methyl ethyl ketone to a pinacol. (b) Give, in detail, the steps involved in the rearrangement of this pinacol to a pinacolone.

13. Prepare a chart showing the synthetic relations of the following compounds to each other and to ethylene, from which all of them are manufactured: acrylonitrile, Cellosolve, Cellosolve acetate, diethylene glycol, dioxane, ethanolamine, ethylene chlorohydrin, ethylene cyanohydrin, ethylene glycol dinitrate, ethylene oxide.

14. Give the reactions involved in the production of glycerol from propene.

15. (a) What is the essential difference in structure between nitroglycerin and the true nitro compounds? (b) What is the chief resulting difference in chemical properties? (c) Write the structural formulas of two isomeric compounds that are glycerol mononitrates and of two that are glycerol dinitrates.

16. (a) What is dynamite? (b) Explain why the substitution of wood pulp for Nobel's infusorial earth is an advantage. (c) Why is the freezing of dynamite an industrial hazard and what means are used by the manufacturer in order to avoid it? (d) Why is the incorporation of ethylene glycol dinitrate especially desirable for this purpose?

17. (a) Explain in detail the origin of the "force" of an explosive. (b) Explain why dynamite is not used as a propellant. (c) Under what conditions is nitroglycerin used in propellant explosives?

18. Assume that a certain explosive, confined in a cube 10 cm on the edge, gives rise on detonation to 30 moles of gas. What would be the pressure developed if the temperature of the gas were: (a) 273°C? (b) 4350° abs?

19. Define the terms: "glyceride"; "triglyceride"; "mixed glyceride"; "mixture of glycerides"; "fat."

20. (a) Assuming a triglyceride containing three different fatty acid radicals, R^1 , R^2 , and R^3 , write the structural formulas of all the possible isomers. (b) Give the names and full structural formulas of the five acids that occur most abundantly in the fats and fatty oils. (c) Compare these acids as to differences in physical and chemical properties. (d) Why is castor oil the only common oil that reacts with considerable quantities of acetic anhydride?

21. (a) Distinguish between the fats and fatty oils on the bases of physical properties and of chemical constitution. (b) Summarize the physical properties which are common to the fats and the fatty oils.

22. Give the names and origins of the more important animal fats and vegetable oils and briefly outline the general methods for obtaining them from natural products.

23. (a) Write the full structural equation for the alkaline hydrolysis of a typical triglyceride. (b) Explain why the hydrolysis of esters is called "saponification." (c) Distinguish between the terms "saponification" and "emulsification."

24. (a) Define the term "soap" and outline its method of manufacture. (b) Explain the detergent action of soap. (c) Explain why the "natural" soaps are ineffective in hard water, in sea water, and in acid solutions.

25. Taking palmitin (mol. wt. 807) as a typical fat, calculate: (a) its percentage of oxygen; (b) the weight of glycerol which would be formed by the saponification of 2000 pounds; (c) the weight of soap (sodium palmitate) which could be obtained by the saponification of 2000 pounds of palmitin, assuming 30 per cent moisture in the soap and 5 per cent loss in manufacture.

26. (a) Describe the manufacture of the three important types of anion-active synthetic detergents. (b) Give examples of cationic and nonionic detergents. (c) Explain accurately why synthetic detergents have advantages over natural soaps under the conditions listed in question 24c.

27. (a) What is meant by the hardening of oils? (b) Explain the chemistry of the process and summarize the practical procedures.

28. (a) Describe the chief uses of linseed oil and explain the property upon which these uses depend. (b) Explain just how the drying of paint differs from the drying of a pyroxylin lacquer (Sec. 18-23).

29. (a) Write the structural formula of a typical phospholipide. (b) What are waxes?

30. Calculate the iodine number of a triglyceride formed from an acid of the composition $C_{12}H_{22}O_2$.

CHAPTER 17

STEREoisomerism; Optical Activity

Compounds which differ only in the arrangement of their atoms in three-dimensional space are called *stereoisomers* (Gr. *stereos*, solid, occupying space). Broadly speaking, this term includes geometrical isomers (Sec. 15-24). More commonly it is restricted to isomers which result from molecular asymmetry. This is usually accompanied by optical activity.

17-1 Asymmetry. An object is *symmetrical* if it can be divided by a plane into two parts that are *mirror images*. A symmetrical object, e.g., a brick, a regular tetrahedron, or an ordinary chair, is also identical with its own mirror image and can be superimposed upon it.

An unsymmetrical or asymmetric¹ object has no plane of symmetry and cannot be superimposed on its own mirror image. A chair with a writing arm on the right cannot be sawed into mirror-image halves and, when observed in a mirror, the writing arm appears on the left. The human hand also is unsymmetrical for the mirror image of a right hand fits a left glove. As a further illustration, examine the key to almost any cylinder lock.

17-2 Molecular Asymmetry. The origin of asymmetry in *molecules* is explained most readily with the aid of conventional wooden models. Let us regard these, first, as exactly what they are—assemblies of balls and sticks. Figure 17-1 pictures such a model in which the central ball, with four sticks extending from it at equal space angles ($109^{\circ}28'$), has colored balls attached—blue *B*, white *W*, and two yellow balls, *Y*¹ and *Y*². Such a model could be sawed in the plane indicated by the vertical line—which is the projection of a plane of symmetry—into halves which are mirror images. It is apparent also—or readily becomes apparent when one uses the actual models—that only *one* arrangement is possible so long as two of the balls are alike.

Consider now the results of replacing one yellow ball by a red one, *R*, so that all four are different. Depending on whether *Y*¹ or *Y*² is thus replaced, the two models pictured in Figure 17-2 are obtained. These are different—one cannot be superimposed on the other; they are related

¹ The Greek prefix *a* (or *an* before a vowel sound) is used to convey the meaning *not* or *without* in many words such as *aseptic*, *asexual*, *anhydrous*, etc.

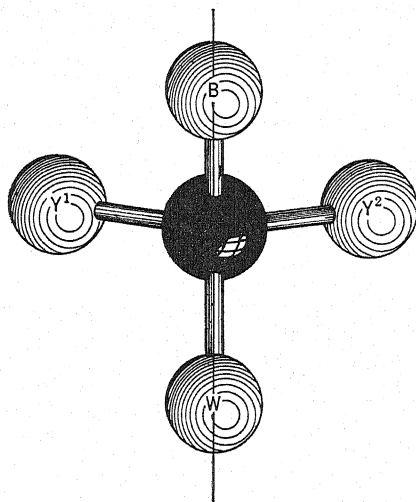


FIG. 17-1 Model showing projection of the plane of symmetry (vertical line) which can always be passed when two of the balls, Y^1 and Y^2 , are of the same color.

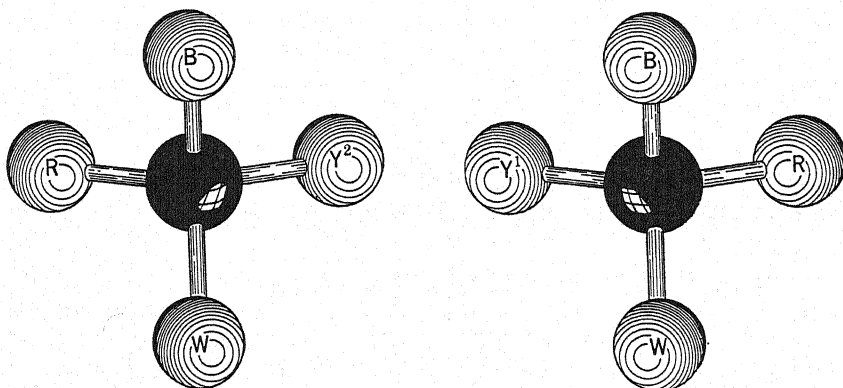
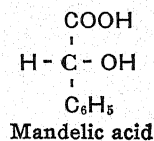
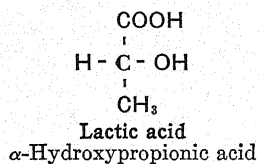
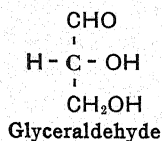


FIG. 17-2 Asymmetric, mirror-image models become possible when balls of *four* different colors are joined to the central ball.

as an object and its mirror image; and neither model has a plane of symmetry.

This reasoning from ball-and-stick models can be transferred directly to molecular structures. In each of the following compounds four different atoms or groups are attached to the α carbon atom:



If now we replace the letters *W*, *B*, *Y*, and *R* of Figure 17-2 by the appropriate chemical symbols, it is apparent that the atoms and groups in each of these molecules can be arranged about the α carbon atom in two different ways. Thus we are led to predict, for example, the existence of two α -hydroxypropionic acids (lactic acids). These two acids are well known. The difference in their structures may be shown either by models or by placing the group symbols at the vertices of a regular tetrahedron¹ as in Figure 17-3.

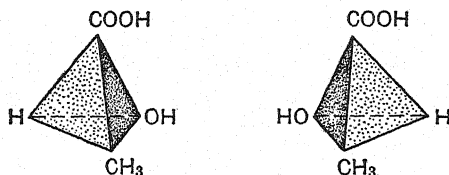


Fig. 17-3 Tetrahedral models representing the stereoisomeric lactic acids. The α carbon atom, not shown, is regarded as situated at the center of the tetrahedron (cf. Fig. 4-3).

17-3 Stereoisomers. The two lactic acids form a typical pair of stereoisomers. Their only structural difference is in their *configurations*—that is, the spatial arrangements about the α carbon atom. Many other pairs of stereoisomers originate in the same way. The requirement is the presence of an asymmetric atom. A carbon atom is described as *asymmetric* if it has four different atoms or groups attached. If a molecule contains only one such atom, two and only two stereoisomers are possible and these are related to each other as an object and its mirror image.

Pairs of *mirror-image isomers* (enantiomorphs) resemble each other closely in all their chemical and in most of their physical properties. Within the limits of experimental error they have identical melting points, boiling points, heats of combustion, and—if acids or bases—ionization constants. Occasionally they crystallize in somewhat different forms, and they commonly differ in their relations toward living organisms. Their most important difference is in optical activity; if one of a pair of mirror-image isomers rotates the plane of polarized light to the *right*, the other rotates it equally to the *left*.

17-4 Optical activity is the power to rotate the plane of polarized light. For the present purpose, *polarized* light may be defined as light *vibrating in a single plane* (actually, in a series of *parallel* planes). It is convenient to think of this plane as being vertical.

¹ It is interesting to note that the conception of the tetrahedral carbon atom (Sec. 4-5), which is now the cornerstone of structural organic chemistry, was first advanced as a *hypothesis* to explain the facts of stereoisomerism (Sec. 17-19).

When polarized light passes through a quartz plate or through a solution of an optically active organic compound, its plane is bent toward the left or toward the right and the light that emerges vibrates in a different plane. The inclination of the latter to the plane of the incident light is measured in angular degrees and is described as the *degree* of rotation.

Substances that rotate the plane of polarized light to the right are called *dextrorotatory* and those which rotate to the left *levorotatory*; those which do not rotate are *optically inactive*. The direction and magnitude of rotation of a liquid or a solution are determined in the polarimeter and the results expressed in angular degrees as the specific rotation. Rotation to the right is indicated by a plus sign before this numerical value or by the prefix *dextro* in the name (*e.g.*, *dextro*-lactic acid); rotation to the left is indicated similarly by a minus sign or the prefix *levo*.

The use of the abbreviations *d*- and *l*- to indicate the direction of rotation is now discouraged because they tend to confusion with the small capitals *D* and *L* which are used with a different meaning (Sec. 17·9). The practice of writing *d*- and *l*- was formerly universal and is still widespread; it is unobjectionable in connection with inorganic crystals.

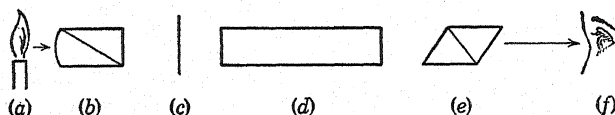


FIG. 17·4 Diagram showing the essential parts of the polarimeter. (a) Source of monochromatic light; this is usually that of the sodium flame which emits radiation of 5890 Å and 5896 Å, corresponding to the *D* lines of the solar spectrum. (b) The *polarizer*—a Nicol prism of calcite so cut and mounted that it transmits light vibrating in a single plane. (c) Semicircle of quartz covering half the field of vision; its function is to give a divided field for accurate comparisons of brightness. (The principle is explained in textbooks of physics.) (d) Covered trough in which can be placed a tube with plane glass ends containing the liquid or solution under examination. (e) The *analyzer*—a second Nicol prism mounted in a housing which can be turned to the right or left; it carries an arm which passes over a circular brass scale divided in angular degrees. (f) The eye of the observer.

17·5 Polarimetry. The optical activity of liquids and solutions is measured in the polarimeter. Figure 17·4 indicates the essential parts of a simple type of this instrument. When properly adjusted, the axes of the polarizing and analyzing Nicol prisms are parallel, the "field" viewed through the eyepiece is uniformly illuminated, and the movable arm of the analyzer rests on the zero of the scale. If, under these conditions, an optically active substance is placed in the trough between the prisms, half of the field is darkened. By turning the analyzer to the right or left, as may be necessary, the field is restored to uniform brightness. The angle through which the analyzer has been turned (read from the position of the arm on the brass scale) is equal to that through which the plane of polarized light was rotated by the substance between the prisms.

Specific Rotation. The observed degree of rotation of a substance in solution depends upon the total number of molecules through which the light passes, and this varies both with the concentration of a solution and with the length of the column in the path of the light. In order to make comparisons, observations are reported in terms of *specific rotation*. This is defined as the rotation in angular degrees of a solution containing 1 gram of solute in 1 cubic centimeter, examined in a tube 1 decimeter in length. It is customary also to specify the temperature and the source of light, D indicating the sodium flame. The symbol for specific rotation is the Greek letter α ; thus, for cane sugar,

$$[\alpha]_D^{20} = +66.5^\circ$$

17-6 Molecular Asymmetry and Optical Activity. Many *crystals*, both organic and inorganic, are optically active although their molecules contain no asymmetric atom. These often occur in two crystalline forms which are mirror images, *e.g.*, *d*- and *l*-quartz (Fig. 17-5), and X-ray

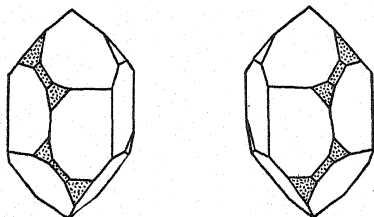


Fig. 17-5 Mirror-image crystals of *d*-quartz and *l*-quartz.

analysis always discloses an unsymmetrical, though *regular*, arrangement of the atoms in the crystal lattices. When this orderly arrangement is destroyed by melting, or by passing into solution or into an amorphous state, optical activity disappears; thus if a crystal of *l*-quartz is dissolved and the identical chemical compound, SiO_2 , is precipitated, the resulting

amorphous powder is optically inactive. Hence, the activity of such substances must be ascribed to an asymmetry maintained solely by the crystal forces.

Compounds that contain an asymmetric *atom* differ from the crystals just described in that they *retain their optical activity in the liquid state, in solution, and in the form of vapor* (if volatile). But, in these states of matter, molecules are in rapid and utterly random motion and there is no possibility of any permanent arrangement with respect to one another. Hence, their activity must originate *within the individual molecule*. In other words, the optical activity of such substances is the result of *molecular* asymmetry. The commonest source of molecular asymmetry, and therefore of optical activity, is an asymmetric *carbon*¹ atom. There exist also certain optically active organic compounds in which asymmetry results from the structure of the molecule as a whole and cannot be assigned to any particular carbon atom (Secs. 17-17, 22-17).

17-7 Racemic Mixtures; External Compensation. In most *laboratory* syntheses in which a compound containing an asymmetric carbon atom is

¹ Optically active compounds are known in which molecular asymmetry arises from the arrangements of different groups about polyvalent atoms of the following elements: S, Se, Te, N, P, As, B, C, Si, Sn, Be, Al, Fe, Cr, Co, Cu, Zn, Ni, Pd, Rh, Ru, Ir, Pt.

made from a compound which has none, the product obtained is optically inactive. This can be understood by considering a typical example such as the preparation of α -chloropropionic acid by chlorinating propionic acid. When *either* hydrogen atom on the α carbon is replaced by chlorine, this carbon atom becomes asymmetric. Depending on *which* hydrogen atom (H^1 or H^2) is substituted there will result one form or the other of α -chloropropionic acid (Fig. 17-6). But H^1 and H^2 on the α carbon of

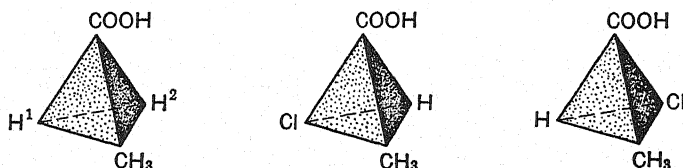
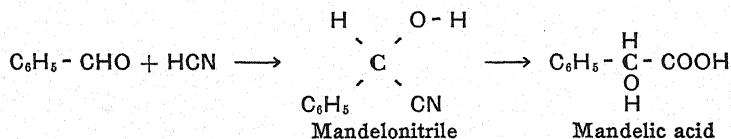


FIG. 17-6 Origin of racemic mixtures. Propionic acid and the stereoisomeric α -chloropropionic acids which it yields on monochlorination.

propionic acid are identical, and substitution proceeds according to the law of chance. Hence there results a mixture of substantially equal numbers of *dextro*- and *levo*-rotating molecules. Such a mixture is optically inactive because the rotation of one kind of molecule is compensated (balanced) by the *equal but opposite* rotation of its mirror-image isomer. This result is entirely comparable to the fact that polarized light shows no rotation if passed successively through equally thick plates of *d*- and *l*-quartz. Optical inactivity having this origin is described as due to *external compensation*. Optically inactive mixtures consisting of equal parts of mirror-image isomers are called *racemic* mixtures and are usually indicated by the prefix DL (or *dl*).

A further example is furnished by the addition of hydrogen cyanide to benzaldehyde. This gives a racemic mixture of mandelonitriles¹ which, on hydrolysis, is converted into an optically inactive mixture of *dextro*- and *levo*-mandelic acids:



Depending on *which* bond of the $\text{C}=\text{O}$ linkage in benzaldehyde is opened, addition of HCN occurs in the two ways indicated in Figure 17-7. Actually it appears that the carbonyl double bond opens on one side or the other, in different molecules, in accordance with the law of chance. The

¹ This is not true if HCN is added to benzaldehyde in the presence of certain optically active alkaloids; *e.g.*, with quinine present, the nitrile formed is prevailingly the *levo* form—a *partial* asymmetric synthesis.

mandelic acids formed by hydrolysis of the CN group have the same configurations as the nitriles.

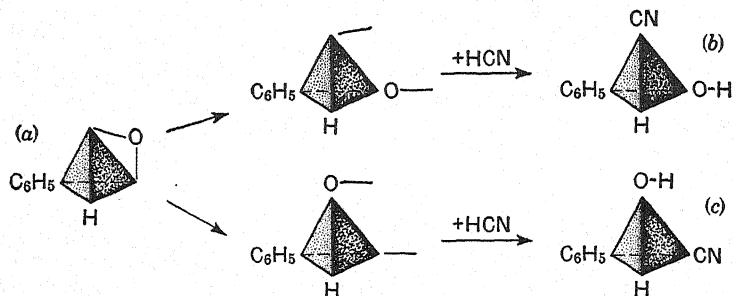


FIG. 17-7 Origin of racemic mixtures in the cyanohydrin synthesis. Benzaldehyde (a) and the *dextro*- and *levo*-mandelonitriles (b) and (c) which it yields by addition of hydrogen cyanide.

17-8 Resolution of Racemic Mixtures. The separation of a racemic mixture into its optically active components is generally called its *resolution*. On account of the identical physical properties of mirror-image isomers, ordinary laboratory methods such as fractional distillation are useless for this purpose. Occasionally the crystals of the two forms show recognizable differences and can be separated by hand under a lens (cf. Sec. 17-19). Another method depends on the selective action of molds and other microorganisms. For example, when a solution of racemic mandelic acid is inoculated with common green mold (*Penicillium glaucum*), the organism feeds upon and thus removes the *levo* acid much more rapidly than its isomer; hence, after some days, the solution contains only *dextro*-mandelic acid, which can be separated and crystallized in the usual way. This method has the obvious disadvantage of destroying at least half of the material.

The most general method of resolution depends on the formation of chemical compounds with another asymmetric substance. Thus the solution of a racemic acid may be treated with an optically active base such as the alkaloid brucine (which is *levorotatory*). There will result the two salts:



These salts are not mirror-image isomers and therefore differ in various physical properties; usually one is appreciably more soluble than the other and they can be separated by fractional crystallization like other compounds. In a similar way, a racemic mixture of active bases can be resolved by forming salts with an asymmetric acid. Alcohols can be resolved by esterification with optically active acids.

All three of these methods for resolving racemic mixtures were devised and used by Pasteur.

17-9 D and L Series of Compounds. It is often observed that optical rotation is changed both in magnitude and in direction when a molecule enters into very simple reactions which do not alter the configuration about an asymmetric carbon atom. For example, a *levorotating* acid may give a *dextrorotatory* sodium salt and ethyl ester, and vice versa. This is one reason which makes desirable a classification based on *configuration*, rather than on the direction of rotation.

The reference standard in the accepted system is the *dextrorotatory* form of glyceraldehyde.¹ This is arbitrarily assigned the configuration

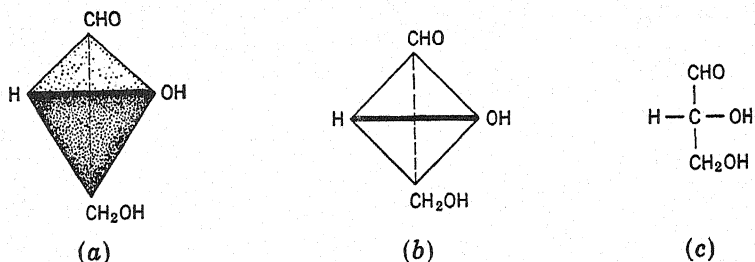
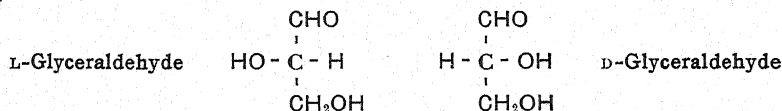


FIG. 17-8 The configuration of *D*-glyceraldehyde may be indicated in these three ways. The heavy horizontal line in (a) and (b) represents an edge of a tetrahedron projecting out toward the observer. If we imagine the tetrahedron as being squeezed into the plane of the paper, we obtain the projection formula (c).

indicated by the formulas of Figure 17-8, in each of which *the hydroxyl group is shown on the right*. *Dextrorotatory* glyceraldehyde is designated by a small Roman capital *D* before its name and its mirror-image isomer by the letter *L*:



Any other compound which can be shown to have the same configuration as *D*-glyceraldehyde is assigned likewise to the *D* series, *regardless of the direction of its rotation*. For example, the *levorotatory* lactic acid formed in the fermentation of sugars by certain microorganisms belongs to the *D* series. The direction of its rotation is shown, when necessary, by writing

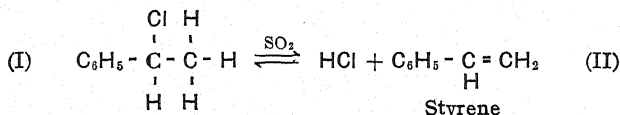
¹ Glyceraldehyde was selected as the primary reference standard because it is the simplest compound having the essential structure of a sugar (Chap. 18). The choice of placing the OH on the right for *dextrorotatory* glyceraldehyde is purely conventional. We still have no sure method for determining the *absolute* configuration of any compound, though progress in that direction is being made.

D-(−)-lactic acid. The isomeric sarcolactic acid, found in muscle, is L-(+)-lactic acid.

In assigning compounds to the D or L series by relating them to the corresponding glyceraldehydes, certain types of reactions must be avoided. These are reactions which involve either a racemization or a reversal of configuration (Walden inversion).

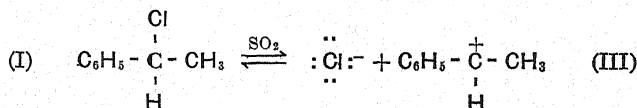
17·10 Racemization is the conversion of half of an optically active compound into its mirror-image isomer. If the reaction is complete, the product is optically inactive. The ease with which racemization can be brought about—by heat, catalysts, and chemical reagents—varies widely among different types of compounds. The optically active halide (I) affords an example. If either its dextro or levo form is dissolved in liquid sulfur dioxide, it is racemized (with a half-life of 18 hours at 0°C). There is evidence for each of the following mechanisms, both of which illustrate possible paths for many other racemizations.

One mechanism assumes the alternate splitting out and addition of hydrogen chloride:



In the intermediate styrene, *asymmetry has been lost through double-bond formation*; when HCl recombines, it does so by the law of chance (cf. Fig. 17·7) and dextro and levo molecules of (I) are formed in equal numbers.

In the alternate mechanism it is assumed that only chloride ion is eliminated, leaving the transitory carbonium ion (III):



X-ray measurements on crystalline calcium carbonate (calcite and aragonite) show that the carbon and three oxygen atoms of the CO_3^- ion lie in a plane. There is much evidence also for this planar arrangement when only three atoms or groups are attached to a carbon atom in a carbonium ion or in a carbanion (Fig. 17·9). If we assume that this figure represents the carbonium ion (III), a recombining Cl^- ion could add—with equal probability—on either side of the plane. The product should consist, therefore, of equal numbers of dextro and levo molecules of (I), which is thus racemized.

In summary: *Racemization is to be expected if at any time during a series of reactions a carbon atom loses its asymmetry, either through entering into a*

double bond or through the formation of a transitory carbonium ion or a carbanion.

Like other chemical reactions, racemizations may stop short of completion. If, for example, a compound of the D series racemizes, the product may still contain more molecules of the D than of the L configuration—but it cannot contain more L than D.

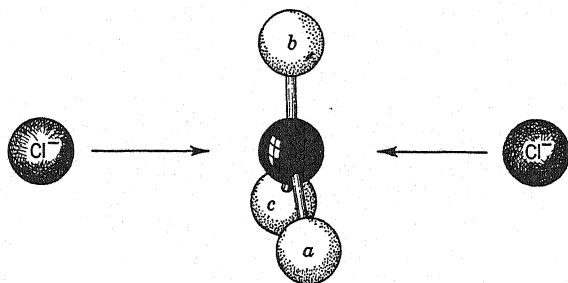
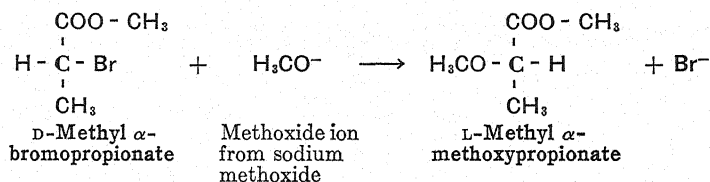


Fig. 17-9 Model indicating the *planar* arrangement of a carbon atom and any *three* attached groups in a carbonium ion or in a carbanion. When a stable molecule is formed through union with an ion of opposite charge, there is equal probability that the latter will add on either side, with racemization. See also Figure 17-10.

17-11 Walden Inversion. In another type of reaction a compound of the D series may be converted completely into a derivative belonging to the L series (or vice versa), *e.g.*,



This is an *inversion of configuration*, usually called a Walden inversion after the chemist who first observed and reported an example (1893). Omitting the long and tedious intervening history, it suffices to outline the mechanism now accepted as the explanation of most Walden inversions.

The reaction in which methoxide, H_3CO^- , ion displaces bromide ion begins with a nucleophilic, back-side attack on carbon (Sec. 7-9). When both H_3CO and Br are attached to carbon, in the transition state, mutual repulsions force the other three groups into a plane with the carbon atom. This is suggested by Figure 17-10, in which *a*, *b*, and *c* may represent H, CH_3 , and CO_2CH_3 . As the H_3CO group continues to approach and bromine recedes, *a*, *b*, and *c* pass over to the opposite side of the plane, where there is more room and less repulsion. Thus the configuration of

the molecule is *inverted*—in a way which has been compared to an umbrella “turning inside out” in a high wind.

The results of many observations may be summarized by the statement that a Walden inversion occurs in every reaction at an asymmetric carbon atom which proceeds by the displacement mechanism just described—that is, a reaction in which the displacing ion is becoming attached while the displaced ion is breaking away. The brominated ester shown above

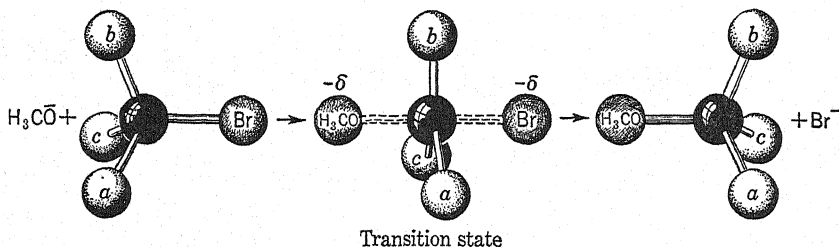
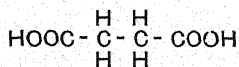


FIG. 17-10 Diagram illustrating the mechanism of the Walden inversion. The inversion of configuration which can be observed when an asymmetric carbon atom is involved affords strong evidence that all other nucleophilic displacements on carbon proceed through a similar transition state. (Adapted from Fieser and Fieser, *Organic Chemistry*, D. C. Heath and Company, Boston, 1950, through the courtesy of the authors and publishers.)

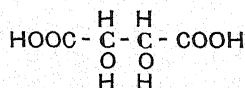
is 100 per cent inverted, but this is an extreme and rather unusual case. More commonly, inversion is incomplete.

COMPOUNDS CONTAINING TWO OR MORE ASYMMETRIC ATOMS

17-12 Active Tartaric Acids. The classic example of stereoisomers containing two asymmetric carbon atoms is furnished by the tartaric acids, $C_4H_6O_6$. Three of these are known (in addition to “racemic acid,” Sec. 17-14), and all have chemical properties which show that they are dihydroxy derivatives of succinic acid.



Succinic acid



Tartaric acids

The last formula shows that the two carbon atoms indicated by the shaded type are asymmetric; one valence of each is used in the linkage between them, while the other three are attached to H, OH, and COOH. The two possible mirror-image configurations are shown in Figure 17-11. If we assume, arbitrarily, that the first of these is dextrorotatory, the other must rotate equally to the left.

A tartaric acid molecule must consist of two of these units—either identical or different. If it contains two dextrorotatory units, each will reinforce the rotation of the other and the molecule is that of *dextro*-tartaric¹ acid (Fig. 17-12). If it consists of two levorotatory units, it is

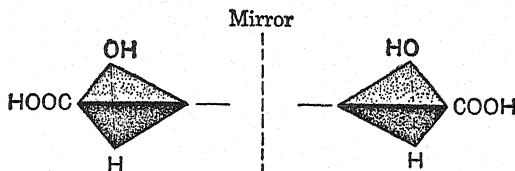


FIG. 17-11 Two possible mirror-image arrangements about the asymmetric carbon atoms in the molecule of a tartaric acid.

levo-tartaric acid (Fig. 17-13). These two figures and the molecules they represent are mirror images, and the compounds have the usual properties of mirror-image isomers. They have the same melting point (170°C), heat of combustion, ionization constant, and solubilities in water and alcohol; their specific rotations are equal, but opposite in sign.

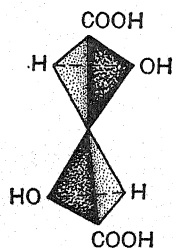


FIG. 17-12.
dextro-Tartaric acid.

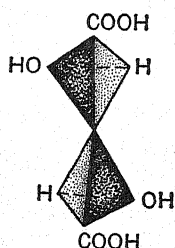


FIG. 17-13.
levo-Tartaric acid.

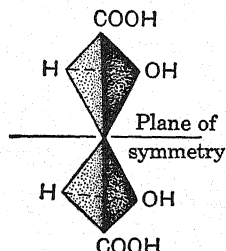


FIG. 17-14.
meso-Tartaric acid.

17-13 *Meso*-tartaric Acid; Internal Compensation. We can imagine a third tartaric acid molecule containing a *dextro*- and a *levorotatory* unit, which would neutralize each other's rotation. The configuration of this optically inactive *meso*-tartaric acid is shown in Figure 17-14. Its molecule possesses a *plane of symmetry* which divides it into mirror-image halves. Such molecules are described as *internally compensated*. Obviously, they cannot be resolved into active components.

Meso-tartaric acid is a stereoisomer of *dextro*- and *levo*-tartaric acids but is not the mirror image of either. It differs from them not only in its lack of optical activity but also in melting point (140 vs. 170°C), solubility relations, and other physical properties. This illustrates the general rule

¹ *Dextro*-tartaric acid, which is the common variety, belongs to the *L* series. This is indicated by the position of the OH group on the lower tetrahedron of Figure 17-12.

that there is no readily predictable relationship between the physical properties of stereoisomers other than mirror-image pairs.¹

17-14 Racemic Compounds (?). When a solution containing both *dextro*-tartaric acid and *levo*-tartaric acid is concentrated by evaporation, crystals of *racemic acid* separate. Examination shows that these crystals are composed of equal numbers of molecules of the *dextro*- and *levo*-acids, into which they dissociate when dissolved; hence, solutions of racemic acid are optically inactive. But, since the crystals differ in form and in melting point (206°C) from the optically active acids (m.p. 170°C), they may be regarded as being composed of a species of chemical compound, analogous to a double salt.

Racemic acid is occasionally obtained, like ordinary *dextro*-tartaric acid, after the fermentation of grape juice. The crystals occur in small clusters, bearing a fancied resemblance to a bunch of grapes. Hence, the name *racemic acid* (L., *racemus*, cluster or bunch of grapes), which was originally applied to this substance and which has since been generalized. Pasteur's resolution of racemic acid into active components is described in Section 17-19.

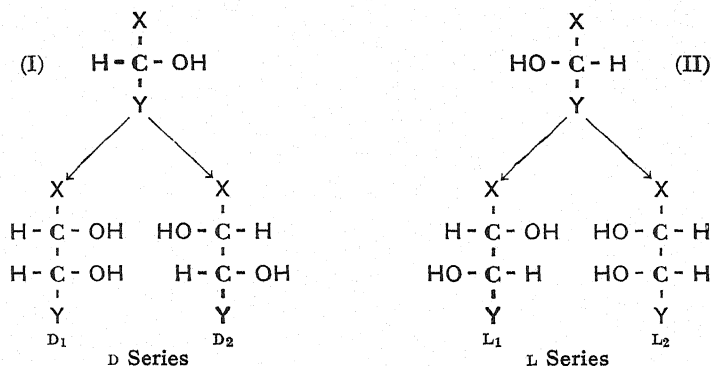
Some other pairs of mirror-image isomers crystallize together and give products which, in the crystalline state, differ in physical properties from their active components. Such crystals are ordinarily known as *racemic compounds*. But in solution these always yield equal numbers of molecules of their active components, which can be separated by the methods already described. Therefore, no special structural formulas are necessary for these so-called compounds.

17-15 Number of Stereoisomers. If a compound contains n asymmetric carbon atoms, the number of stereoisomers theoretically possible is 2^n . This statement is known as van't Hoff's rule. Accordingly, the isomers to be expected with 2, 3, and 4 asymmetric carbon atoms are 4, 8, and 16, respectively (exclusive of any racemic "compounds"). These will consist of 2, 4, and 8 pairs of mirror-image isomers, the members of each pair having equal and opposite rotations. The rule has been verified in many instances, including preparation of the 16 different aldohexose sugars (Chap. 18) for which it calls.

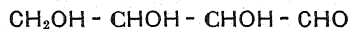
Exceptions to van't Hoff's rule occur when any stereoisomer has a plane of symmetry. The presence of such a plane in the *meso* compound (Fig. 17-14) explains why there are only three tartaric acids instead of the four which the rule predicts. But when one COOH group is esterified, the predicted four isomers are obtainable. If, using models corresponding to Figure 17-14, one replaces by CH₃ the H of the upper COOH group in one model and that of the lower COOH group in another, different models result. These are mirror images, and neither has a plane of symmetry. The monomethyl tartrates which they represent are additional to another pair derived from *dextro*- and *levo*-tartaric acids.

¹ Stereoisomers which are not mirror images are sometimes called *diastereoisomers*.

17.16 Projection formulas¹ may be substituted for the more cumbersome space models in illustrating van't Hoff's rule, in explaining its limitations, and for other purposes. In the following, let X and Y stand for any *unlike* atoms or groups (CHO, CH₂OH, COOH, etc., the only restriction being that neither group may be asymmetric). With a single asymmetric carbon atom, we have the usual D and L pair (I) and (II). Assume now that a second asymmetric group (H—C—OH) is introduced into each of these molecules between C and X. This second group may enter in two ways into (I) and in two ways into (II) as follows:



The four possible stereoisomers consist of two mirror-image pairs, D₁ and L₂, D₂ and L₁. A specific example is furnished by the four stereoisomeric sugars of the formula



in which CHO and CH₂OH correspond to X and Y, respectively. But if the CHO group is reduced to CH₂OH, making X and Y identical, only three alcohols are possible, just as with the tartaric acids.

17.17 Asymmetry in Cyclic Compounds. All the geometrical, *cis-trans* isomers which were described in Section 15.24 have a plane of symmetry and are, therefore, optically inactive. But certain nonbenzenoid ring compounds provide opportunities for both geometrical and optical isomerism. This is illustrated by the *o*-dicarboxylic acids derived from cyclohexane. Regarding the six carbon atoms of the ring as lying in the

¹ When working with *solid* models, it is legitimate to lift them and invert them in the effort to determine whether they can be superimposed (the test for identity). Projection formulas, however, which seek to represent three dimensions in a plane, are subject to greater limitations. They may be rotated in the plane of the paper, *but they must not be lifted out of this plane!*

plane of the paper,¹ some of the hydrogen atoms attached to them must lie above and others below this ring. The two COOH groups, likewise, may be situated either on the same side of the ring (in the *cis* acid) or one

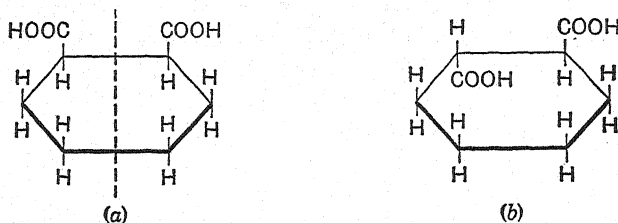


FIG. 17-15. Cyclohexane-*o*-dicarboxylic acids; (a) *cis* acid, m.p. 192°C; (b) *trans* acid, m.p. 215°C.

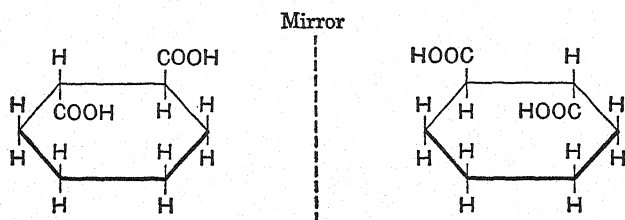


FIG. 17-16. Asymmetric, optically active isomers of *trans*-cyclohexane-*o*-dicarboxylic acid.

above and one below (in the *trans* acid) as represented² in Figure 17-15. Careful inspection of this figure shows that the *cis* acid has a plane of symmetry dividing it into halves that are mirror images; thus, it is internally compensated, is optically inactive, and occurs in only one form. The *trans* acid, on the other hand, has no plane of symmetry and two active mirror-image isomers are known. These are pictured in Figure 17-16.

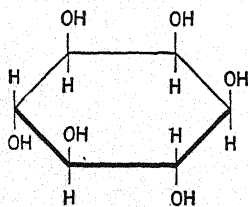


FIG. 17-17. *meso*-Inositol.

Meso-inositol (Sec. 16-15) has been proved to have the structure shown in Figure 17-17. It is one of eight possible *cis-trans* isomers which differ in the relative positions of H and OH above and below the carbon ring, and of OH groups to one another (1,2 or 1,3

¹ The argument here is not changed by the fact that, strictly speaking, the six carbon atoms do not lie in a single plane but have one of the arrangements shown in Figure 4-6, page 60. Each of these, however, is capable of passing readily into the other and, in the course of such a change, must pass through a single-plane phase.

² In figures such as 17-15 it is convenient to allow each angle of the hexagon to represent a carbon atom of the ring. Atoms or groups joined by lines extending upward are regarded as lying above the plane of the carbon atoms, and vice versa. The plane is better visualized by shading its "front."

or 1,4). Several of these inositols occur in nature, and others have been synthesized. One of them lacks a center of symmetry and occurs in optically active, mirror-image forms, making a total of nine space isomers.

17-18 Asymmetry and Life. Pasteur was impressed with the many optically active compounds found in plant and animal bodies, *i.e.*, in *living* organisms. Since his time, examples have multiplied. They include many complex natural products such as the sugars, proteins, terpenes, and alkaloids, as well as numerous simpler compounds.

As a rule, only one of any pair of mirror-image isomers is found in a particular plant or animal, and frequently only one variety (the dextro form of some compounds, the levo form of others) occurs anywhere in nature. It has been observed, also, that mirror-image isomers usually show marked differences in their relations to living organisms. The selective action of the lower organisms has already been referred to as one of the methods for resolving racemic mixtures. A similar effect of structure is often observed when asymmetric compounds are introduced into the bodies of living animals. For example, one form of an optically active drug may have many times the pharmacological action of its mirror-image isomer.

All such observations lead to the conclusion that the forces operating in living organisms are themselves asymmetric. Some factor other than the law of chance is responsible for the fact that, when carbon, hydrogen, and oxygen atoms are combined in the grape to form molecules of a tartaric acid, they do so almost invariably in that unsymmetrical arrangement which produces dextrorotation. Likewise some asymmetrical influence must operate in the body of a rabbit, where *levo*-malic acid is promptly oxidized while its dextro isomer is rejected and excreted unchanged. (See also Section 27-7.) With regard to the actual mechanism of these asymmetric influences and the origin of asymmetric compounds in nature, very little is known.

17-19 Historical. Stereoisomerism is most readily understood by considering it as a logical consequence of the tetrahedral structure of the carbon atom. Historically, however, just the reverse occurred; the observed phenomena of stereoisomerism led to the development of the tetrahedral theory.

Pasteur's resolution of racemic tartaric acid is properly regarded as one of the great landmarks in the history of chemistry. Seeking the origin of the difference between ordinary dextrorotatory tartaric acid and racemic acid, the only varieties then known, he prepared many salts of each without finding any difference in their crystalline forms. But when he prepared the sodium ammonium salts, he observed that the crystals from racemic acid were of two kinds, differing in the right- and left-handed arrangement of the small shaded facets shown in Fig. 17-18. With the aid of a lens and tweezers, Pasteur picked out the two kinds of crystals, dissolved each lot separately, and found that one solution rotated polarized light to the right and the other to the left. On converting the salts into their corresponding free acids, the one that

gave the dextrorotation was found to be identical with ordinary tartaric acid. The other proved to be *levo*-tartaric acid, previously unknown. Later, he obtained *meso*-tartaric acid by heating the salt of *dextro*-tartaric acid and the alkaloid cinchonidine with water at about 165°C.

Before the time of Pasteur, the optical activity of *crystals* had been extensively studied, and it was commonly believed, as much more recent X-ray studies have proved, that this is due to some right- or left-handed unsymmetrical arrangement of the crystal units. Pasteur recognized that this explanation could not apply to optical activity in a solution. In one of his lectures he said: "Consider a spiral staircase, the steps of which are cubes or other objects superimposable upon their mirror images. Destroy the staircase, and the asymmetry disappears. The asymmetry of the staircase was due to the method of placing together the single steps. So it is with quartz Consider, again, the same spiral staircase, the steps of which are formed

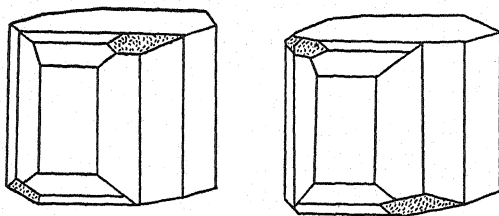


FIG. 17-18. Mirror-image crystals of sodium ammonium tartrates.

of *irregular* tetrahedra. You may destroy the staircase, but the asymmetry remains because you have to deal with a collection of irregular tetrahedra." He advanced far enough to lay down the general principles: "Molecular asymmetry expresses itself in optical activity; reciprocally, optical activity reveals molecular asymmetry"; and "every asymmetric arrangement has its mirror-image opposite of which the chemical properties are exactly the same." But Pasteur recognized that he was groping in the dark with regard to the exact origin of intramolecular asymmetry: "Are the atoms of *d*-tartaric acid grouped in the form of a right-handed helix, or do they stand at corners of an irregular tetrahedron, or are they arranged in some other manner? We are not yet in a position to answer these questions. But it cannot be a subject of doubt that there exists an arrangement of the atoms in an asymmetric order, having a nonsuperimposable image."

After working on the tartaric acids from 1848 to 1853, Pasteur's interests were diverted to other fields. A quarter of a century later, organic chemistry had progressed far enough to give the answer to his question. In 1874, within a few months of each other and quite independently, Le Bel (France) and van't Hoff (Holland) advanced slightly different forms of the theory of the tetrahedral carbon atom. The validity of this theory has been confirmed by all subsequent work, including the X-ray analysis of crystals.

Louis Pasteur (1822–1895) was one of the most distinguished scientists of all time. Trained primarily as a chemist, he early developed that interest in crystallography which led to his work on molecular asymmetry. From this he was drawn away by his country's need to studies on the nature and origin of fermentation. In this connection he devised the treatment known as *pasteurization*, for the preservation of wine; this is now widely used for milk. From fermentation, he was led to develop the germ theory of disease and, thence, to the serological treatment of rabies (hydrophobia)

which goes by his name. He is properly regarded as the founder of two great branches of modern medical science—bacteriology and serology.

Questions

1. Define the terms: (a) "symmetrical" and "unsymmetrical"; (b) "polarized light"; (c) optical activity"; (d) "dextrorotatory" and "levorotatory"; (e) "specific rotation"; (f) "asymmetric carbon atom"; (g) "configuration"; (h) "plane of symmetry."

2. (a) Draw the space models which show that four balls of unlike colors can be arranged in two ways when attached to the vertices of a regular tetrahedron and show that both of these are unsymmetrical. (b) Using the same drawings, substitute the appropriate symbols and account for the existence of two stereoisomeric mandelic acids.

3. (a) Write the structural formula of one α -hydroxy acid and of one α -amino acid, both of which are optically inactive. (b) Show why all other α -monosubstituted acids of these types necessarily exist in two asymmetric forms.

4. Carefully define, illustrate, and distinguish between the meaning of the following terms: (a) "isomers"; (b) "chain isomers"; (c) "position isomers"; (d) "stereoisomers"; (e) "mirror-image isomers."

5. Summarize the relations between the physical and chemical properties of mirror-image isomers and emphasize the chief difference. Do these relations hold for stereoisomers that are not mirror images?

6. Account for crystalline asymmetry and explain why this explanation is inadequate to account for compounds that retain their optical activity in solution and in the form of vapor?

7. Define "racemic mixture," "racemization," and "external compensation."

8. Explain with the aid of drawings why racemic mixtures are obtained: (a) when one hydrogen atom on the α carbon of butyric acid is substituted by bromine; (b) when hydrogen cyanide adds to butyraldehyde; (c) when hydrogen chloride adds to 2-methyl-1-butene.

9. (a) Describe and illustrate the three methods for resolving racemic mixtures. (b) The alkaloid cinchonine is a dextrorotatory base; explain just why the salts which it forms with a solution of racemic mandelic acid are neither identical nor mirror-image isomers.

10. Differentiate carefully between a racemization and a Walden inversion and explain a mechanism for each.

11. Make tetrahedral drawings to account for the existence of three stereoisomeric tartaric acids (exclusive of racemic acid).

12. Explain by the use of such drawings why there are four stereoisomeric monomethyl tartrates although only three tartaric acids.

13. Given the space model or projection formula of a compound containing two or more asymmetric carbon atoms, explain how it is possible to tell, by inspection, whether or not the compound is optically active?

14. State van't Hoff's rule, illustrate it, and account for exceptions.

15. Write the projection formulas of two pentahydric alcohols which are: (a) optically active; (b) optically inactive through internal compensation.

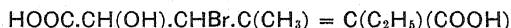
16. Mark the asymmetric carbon atoms in the following, predict the number of possible stereoisomers of each, and write projection formulas for any which would be optically inactive through internal compensation:

- (a) $\text{CH}_2(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{CHO}$
- (b) $\text{CH}_2(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{CH}_2(\text{OH})$.
- (c) $\text{CH}_2(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\text{OH}$.
- (d) $\text{CH}_2(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{CH}_2(\text{OH})$.
- (e) $\text{CH}_2(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{CH}(\text{OH})\cdot\text{CHO}$.

17. (a) Give examples of compounds that are stereoisomers but not mirror images. (b) What simple relation, if any, exists between the rotatory powers of stereoisomers that are not mirror images? (c) How do the other physical and chemical properties of such compounds compare with those of mirror-image pairs?

18. (a) Explain why most geometrical isomers are optically inactive. (b) Explain the optical activity of *o*-disubstitution products of cyclohexane which have the *trans* configuration and the inactivity of the isomeric *cis* compounds.

19. Considering any asymmetric carbon atoms in the following compound and the possibility of *cis-trans* isomerism, what is the total number of space isomers to be expected?



Defend your answer by the use of projection formulas.

20. A certain water solution is placed in a polarimeter and found to be optically inactive. Give three different *types* of solutes of which this could be true, with a specific example of each.

21. (Voluntary exercise.) Make drawings similar to Figure 17-17 showing the eight *cis-trans* inositols. Designate the one which is optically active and can exist in dextro- and levorotatory forms.

CHAPTER 18

CARBOHYDRATES

It is estimated that three-quarters of the dry weight of the plant world is composed of organic compounds known as *carbohydrates*. These include the sugars, starch, and cellulose. Sugars are found in the sap of all plants; starch is the chief component of seeds, bulbs, and tubers; fibers, leaves, stalks, and trunks are composed mainly of cellulose.

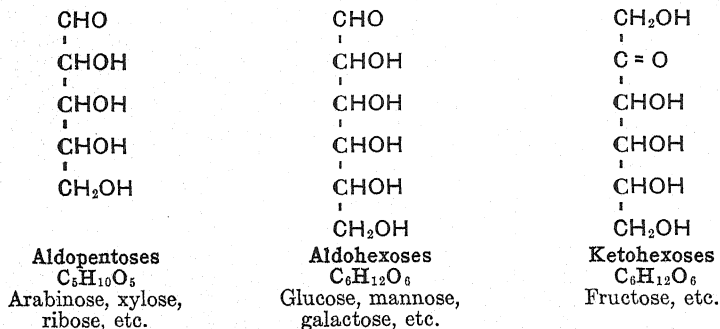
The carbohydrates are of primary importance to man on account of their industrial and biochemical relations. Plant cultivation—agriculture—has always been the world's greatest industry and must long retain that position. This is due to the demand for its products as food for man and his domestic animals. But the carbohydrate products of plant life also serve as the raw materials for many other important industries. These include the manufacture of paper and cotton textiles, ethyl alcohol and other products of fermentation, and the cellulose esters used for making explosives, rayon, lacquers, and photographic film.

The only information available to the earlier chemists about the chemical nature of the carbohydrates was that furnished by elementary analysis. This showed that, besides carbon, they contained hydrogen and oxygen *in the proportion to form water*. For example, the composition of glucose could be expressed by the formula $C_6(H_2O)_6$. Since such formulas bore a certain resemblance to those of the inorganic hydrates, *e.g.*, blue vitriol, $CuSO_4 \cdot 5H_2O$, the compounds were thought of as *hydrates of carbon* and were called *carbohydrates*.

MONOSACCHARIDES OR SIMPLE SUGARS

18-1 Monosaccharides are carbohydrates that cannot be hydrolyzed to simpler compounds. All the important ones can be represented by the general formula $(CH_2O)_n$, where n is either 5 (*pentoses*) or 6 (*hexoses*).¹ For many purposes, they may be regarded as aldehyde or ketone derivatives of higher polyhydric alcohols, and on this basis they are divided into *aldoses* and *ketoses*. Disregarding stereoisomerism for the present, the structures of the important naturally occurring monosaccharides can be represented by the following plane formulas:

¹ The systematic names of all sugars and most other carbohydrates end in *-ose*. Note that the general formula $(CH_2O)_n$ includes some noncarbohydrates such as formaldehyde, acetic acid, and lactic acid.



All the sugars are colorless crystalline solids. They are freely soluble in water and are able to diffuse through animal membranes and the walls of plant cells. They are sparingly soluble in absolute ethyl alcohol and practically insoluble in ether and hydrocarbons. All are sweet but in varying degrees. They cannot be melted or distilled since they are decomposed (caramelized) by heating. All are optically active.

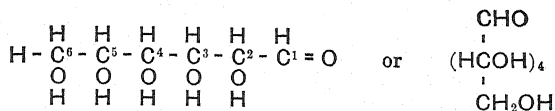
Glucose is a typical simple sugar and the most important carbohydrate of that class. For this reason it will be discussed in some detail.

18-2 Glucose, C₆H₁₂O₆, occurs in the sap of most plants and is especially abundant in the juice of grapes.¹ It is present also in small but nearly constant amount in animal blood. Glucose is one of the hydrolysis products of milk sugar and cane sugar and the sole *end* product of the hydrolysis of maltose, cellobiose, starch, glycogen, and cellulose. Thus it is the chief product of digestion of carbohydrate food in the animal organism, where it serves as the major source of energy and body heat. Much glucose is also present in molasses; this is fermented by microorganisms for the production of ethyl alcohol, butanol, citric acid, etc.

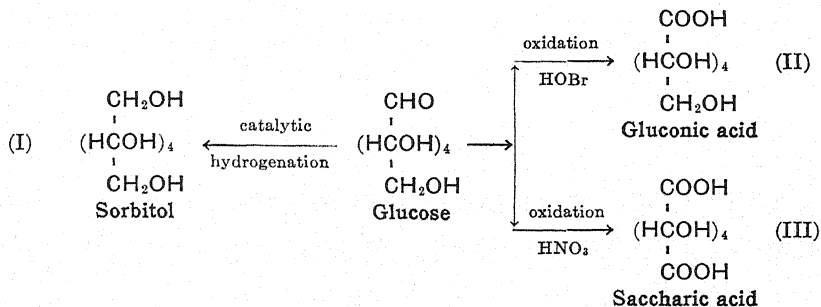
Glucose is manufactured in large quantities by hydrolyzing starch (cornstarch in America, potato starch in Europe) with steam and dilute acid. It is sold in crystalline form, known in this country as corn sugar or *cerulose*, and as a concentrated solution, *corn syrup*. Glucose is only about three-fourths as sweet as ordinary table sugar (sucrose). Major uses are in the manufacture of confectionery and preserves and in bread-making; in the baking industry its fermentation by yeast gives rise to the carbon dioxide that leavens the bread.

18-3 Chemical Properties and Structure. Many of the chemical properties of glucose are suggested and explained by the open-chain formula

¹ For this reason it is sometimes called *grape sugar*. Glucose is dextrorotatory, and another common name is *dextrose* (contraction of *dextroglucose*). It is properly described as D-glucose (Sec. 18-6).



which represents it as a typical aldohexose. Catalytic hydrogenation reduces it to a hexahydric alcohol (I). Glucose forms a pentaacetate, showing that it contains five OH groups; no two of these can be attached to the same carbon atom since the sugar does not easily lose water. Glucose adds hydrogen cyanide to form a cyanohydrin—evidence for a carbonyl group. When the CN group is hydrolyzed to COOH and all OH groups are reduced (by the action of hydriodic acid¹), the product is *normal* heptanoic acid. This proves that glucose contains a nonforked carbon chain and that the C=O group is aldehydic. The position of the carbonyl group is confirmed by the oxidation of glucose to the *six*-carbon acids (II) and (III):

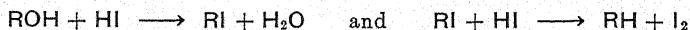


Other chemical properties which are important, though not involved in the proof of structure, are the formation of osazones and reducing action.

18-4 Osazones. Both aldoses and ketoses react with phenylhydrazine like the simple aldehydes and ketones, but the resulting *phenylhydrazones* are usually quite soluble in water and consequently are of little value for the separation or identification of the sugars.²

Osazones are far more important derivatives, obtained by heating a solution of the sugar with an *excess* of phenylhydrazine and acetic acid, or phenylhydrazine hydrochloride and sodium acetate. Three reactions

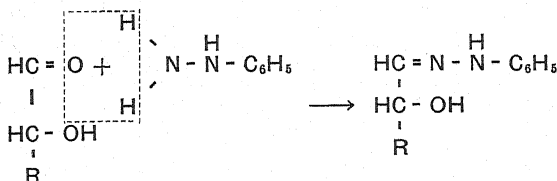
¹ A concentrated solution of hydrogen iodide is a powerful reducing agent which replaces OH groups by hydrogen through the reactions



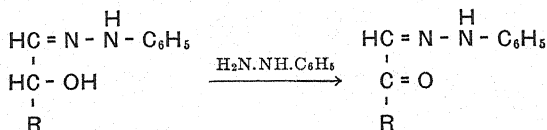
Efficiency is increased in the presence of red phosphorus, through which HI is regenerated from I₂.

² Some sugars yield sparingly soluble, characteristic hydrazones with *p*-nitrophenylhydrazine, *β*-naphthylhydrazine, etc.

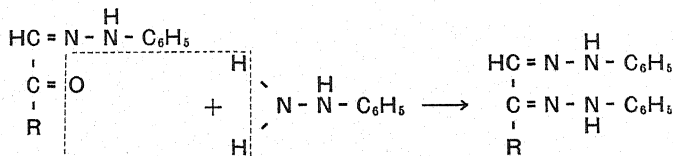
are involved as illustrated in the formation of glucosazone, as follows¹:



(I) Formation of glucose phenylhydrazone (water soluble).



(II) Oxidation of C² to carbonyl by action of a second molecule of phenylhydrazine; the latter is reduced to ammonia and aniline.



(III) Formation of *glucosazone* by action of a third molecule of phenylhydrazine.

The osazones are yellow solids, practically insoluble in water; they can be further purified by recrystallization from hot alcohol or a dilute solution of pyridine. It is thus possible to obtain them in well-defined crystals which may be identified by their melting points or, microscopically, by their characteristic forms. They are therefore very useful for the detection and identification of small amounts of sugars.

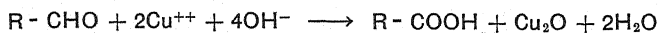
The osazone reaction was discovered by Emil Fischer (1874) who made extensive use of it in the researches in which he established the structures of the aldohexoses. One of his chief difficulties lay in the high water-solubility of the sugars and the fact that, even when their solutions are saturated, they often crystallize with difficulty in the presence of inorganic salts and nitrogeous substances. He therefore converted the sugars into insoluble osazones and purified the latter by recrystallization. The osazone was then boiled with water and a small excess of benzaldehyde; the phenylhydrazine radicals were thus removed as the more insoluble benzaldehyde phenylhydrazone. Filtration gave a solution of the original sugar in substantially pure water which could be concentrated in a vacuum desiccator.

18.5 Reducing Sugars. All simple sugars and the disaccharides other than sucrose reduce alkaline cupric solutions with the precipitation of

¹ Since only C¹ and C² of any sugar are involved in the reactions with phenylhydrazine, the remainder of the molecule is conveniently represented by the symbol R.

cuprous oxide. With the exception of polarimetry, most methods for estimating sugars are based on this reducing action. The usual reagents are Fehling's solution and Benedict's solution (Sec. 20-9), which are used widely for the detection of reducing sugars and for their quantitative estimation in food products, urine, blood, etc.

The reducing action of glucose on alkaline copper solutions cannot be explained in terms of the simple reaction



The weight of Cu_2O precipitated is between two and three times the amount calculated from this equation. Furthermore fructose—a ketose, containing no CHO group—is almost as strongly reducing as glucose.¹ The actual reactions are exceedingly complex. Fehling's solution is strongly *alkaline* and is used at the boiling temperature. Under these conditions the carbon chains of reducing sugars—both aldoses and ketoses—are ruptured, giving highly reactive fragments containing one to five carbon atoms. These fragments are the reducing agents. Hence, reducing power is actually a measure of the *extent of fragmentation* under a given set of conditions.²

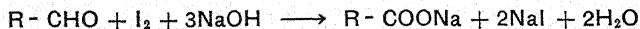
It is important to note that the complex series of reactions involved in alkaline reducing action *begins* at the carbonyl group (actual or potential, Sec. 18-8) of the sugar molecule. When this group is blocked, as in the glycosides (Sec. 18-9), the compounds are nonreducing.

18-6 Stereoisomeric Aldohexoses. Inspection of the plane formula representing any aldohexose shows that carbon atoms 2, 3, 4, and 5 are asymmetric. According to van't Hoff's rule there should be 16 stereoisomers, consisting of eight mirror-image pairs. Only the four of these sugars shown below occur in nature, but the others have been synthesized

¹ The oxidation of *aldoses* by certain reagents is in fact limited to this conversion of CHO into $COOH$. Thus glucose is oxidized to the six-carbon gluconic acid (II, of Sec. 18-3) by bromine water:



and the reaction with sodium hypiodite proceeds quantitatively according to the equation



Under the conditions used in the latter determination, *ketoses* are nonreducing.

² Quantitative determinations of reducing sugars depend upon reproducing accurately a standard set of conditions. When the weight of precipitated Cu_2O has been determined, the corresponding weight of glucose (or of fructose, maltose, or lactose) is read from available tables. These tables are based on standardized experiments with known weights of the pure sugars; a separate table is necessary for each of them.

and the space configurations of all 16 established.¹ The results are expressed by projection formulas such as the following:

				Carbon number (1)
CHO	CHO	CHO	CHO	
H - C - OH	H - C - OH	HO - C - H	HO - C - H	(2)
HO - C - H	HO - C - H	H - C - OH	HO - C - H	(3)
H - C - OH	HO - C - H	H - C - OH	H - C - OH	(4)
H - C - OH	H - C - OH	HO - C - H	H - C - OH	(5)
CH ₂ OH	CH ₂ OH	CH ₂ OH	CH ₂ OH	(6)
D-Glucose	D-Galactose	L-Galactose	D-Mannose	
+52.7°	+80.2	-80.2	+14.2°	

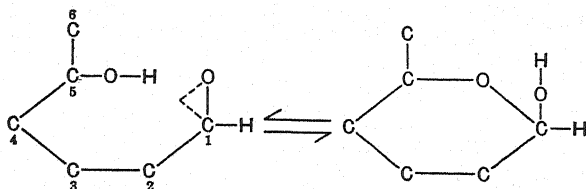
The individual hexoses are assigned to the D and L series (Sec. 17-9) according to their established configurations about the asymmetric carbon atom farthest removed from the carbonyl group (C⁵, in the formulas above). This configuration is that of D-glyceraldehyde (OH on the right) in the three D-sugars; the opposite arrangement is seen in the projection formula for L-galactose.

18-7 Mutarotation. The rotation of a solution of tartaric acid does not change with time, and this is true of most other optically active compounds. But a *freshly prepared* solution of ordinary crystalline D-glucose has a high specific rotation which gradually decreases to +52.7° and then remains constant. This phenomenon is described as mutarotation (L., *muto*, to change). Its origin is as follows:

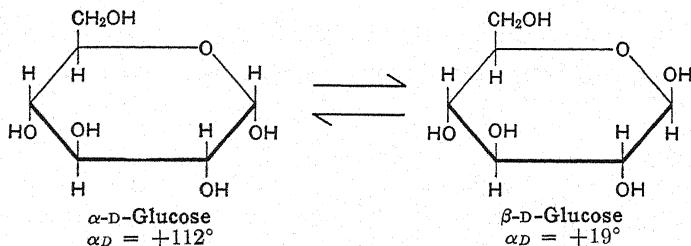
Depending on the conditions, D-glucose crystallizes from solution in two forms. The variety known as α -D-glucose separates, as a monohydrate, at ordinary temperatures from a saturated solution in 70 per cent alcohol. When these crystals are dissolved in water, the initial rotation is $\alpha_D = +112^\circ$, but this decreases on standing to +52.7°. Saturated aqueous solutions at about 98°C yield β -D-glucose (anhydrous). Its solutions give an initial value of +19°, which *increases* to +52.7°. In solution, each form is able to change into the other, and these changes in structure are responsible for the observed changes in optical activity. A solution of *constant* rotation ($\alpha_D = +52.7^\circ$) contains both forms *in equilibrium*. Ordinary crystalline glucose is chiefly the α variety; in solutions at equilibrium, the ratio between the α and β forms is approximately 1:2.

¹ The world is indebted to Emil Fischer (1852-1919) for the series of brilliant researches that clarified the space relations of the sugars. These cover the period 1885 to 1894 and the last three years of his life; in the interim, he performed a similar service with respect to the chemistry of the purine derivatives and the proteins.

18.8 Cyclic Structures. The structural difference between the α and β forms of D-glucose remains to be explained. The key to the problem was the observation that glucose does not give *all* the ordinary aldehyde reactions; its solutions do not redden Schiff's reagent, and glucose reacts very slowly with sodium bisulfite. For this reason Tollens surmised (1883) that relatively few of the molecules have a *free* aldehyde group. Data now available indicate that this is limited to about 0.025 mole per cent. For the most part, glucose exists in the form of *cyclic* molecules—hemiacetals (Sec. 10·7)—formed by an internal addition reaction between the carbonyl group and the alcoholic hydroxyl on C⁵:



But, depending on *which side* the C=O bond opens (cf. Fig. 17·7), the OH group on C¹ of the cyclic molecule will lie either *above* or *below* the plane of the ring, as shown in the conventional formulas¹:

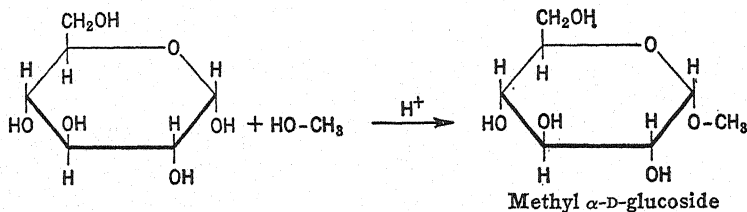


Thus α - and β -D-glucose differ in the two possible space arrangements about C¹, which becomes asymmetric on ring closure.

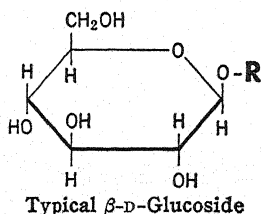
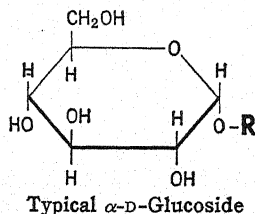
Summarizing: In any water solution which has been allowed to stand, about one-third of the D-glucose present is in *alpha* and two-thirds in *beta* cyclic molecules. These are in equilibrium with a very small amount of the open-chain aldehyde isomer and, through this, are in equilibrium with each other. Probably it is only the aldehyde form which enters into chemical reactions such as osazone formation and reducing action. But, as these aldehyde molecules are removed, more are formed from the cyclic molecules. The sugar may be described, therefore, as containing a *potential* aldehyde group.

¹ Cf. footnote 2, page 336.

18.9 Glucosides are derivatives of glucose in which some radical has replaced the hydroxyl hydrogen on C^1 of a cyclic molecule. The simplest are methyl and ethyl glucosides which are readily formed by dissolving D-glucose in methyl or ethyl alcohol and saturating the solution with hydrogen chloride gas. For α -D-glucose and methanol the reaction may be formulated as follows:



In like manner, β -D-glucose yields the isomeric methyl β -D-glucoside. These are the simplest of many pairs of glucosides which can be represented by the formulas



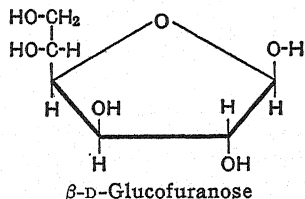
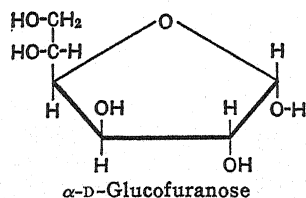
in which R either may be a simple radical such as CH_3 or may be derived from a more complex molecule such as another sugar. All glucosides are readily hydrolyzed by acids to glucose and $R.OH$, the *aglucon*. Enzymes act selectively; some hydrolyze only *alpha* and others only *beta* glucosides.

The simple glycosides never behave as free aldehydes. They are stable toward alkalies, are nonreducing, do not react with phenylhydrazine, and do not exhibit mutarotation. This means that, when the mobile hydrogen of the OH on C^1 is replaced, the molecule cannot change to a free aldehyde form or from one cyclic form to the other.

Glycosides. Derivatives of other sugars, similar to the glucosides, are called galactosides, fructosides, etc. Collectively, all such compounds are referred to as *glycosides*. These compounds are widely distributed in nature. They include the disaccharides and the colloidal carbohydrates, starch and cellulose. Other natural glycosides are the tannins, various compounds responsible for the coloring of certain flowers, and plant products from which important drugs are obtained (*e.g.*, digitalis).

18.10 Pyranose and Furanose Forms. In the cyclic formulas above, ring closure through oxygen is indicated between C^1 and C^5 . Sugars and

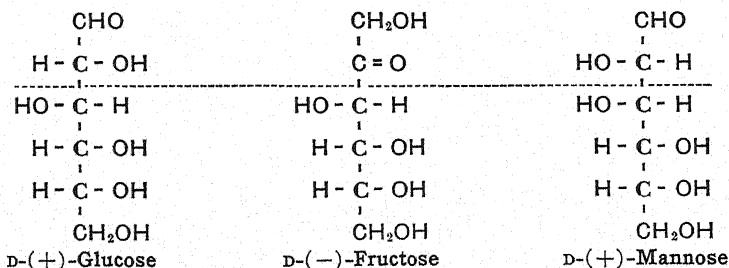
glycosides containing this six-membered ring are described as *pyranose* forms (cf. Sec. 26.5). This is the commonest but not the only ring system. Under some circumstances ring closure occurs between C^1 and C^4 , giving the five-membered *furanose* ring (Sec. 26.9), e.g.,



These furanose forms of D-glucose have not been isolated, but the corresponding ethyl glucosides are known.

18.11 Other Hexoses. The 15 aldohexoses which are stereoisomers of D-glucose, and the ketohexoses (represented by D-fructose) all resemble D-glucose in their general physical and chemical properties. They yield pentaacetates, are fragmented by alkalis, reduce Fehling's solution, and form osazones. Their solutions exhibit mutarotation, arising from the interconversion of α and β cyclic forms, and they yield glycosides corresponding to these forms. Only those which occur in nature are fermentable by yeast.

D-Fructose (levulose) is the best known of the eight possible stereoisomeric *ketohexoses*. Its open-chain projection formula is given below with those of D-glucose and D-mannose, which it closely resembles:

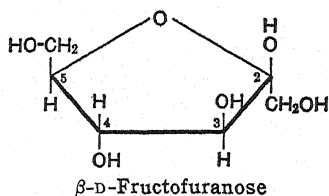
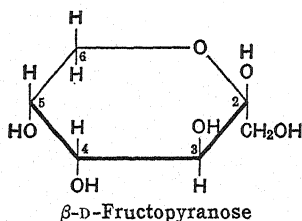


The fact that fructose contains a secondary carbonyl or *keto* group (actual or potential) was established by determining that a *branched* carbon chain is formed when HCN adds to fructose.

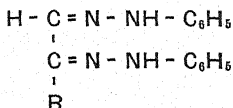
Fructose is extremely soluble in water, forming syrups from which it crystallizes only with difficulty. It is strongly levorotatory; for the equilibrium solution, $\alpha_D = -92.4^\circ$. It is the sweetest of all the sugars; if the sweetness of cane sugar is taken as 100, fructose = 173, glucose = 74, and lactose = 16. This accounts for the peculiar sweetness of honey

(invert sugar, Sec. 18-17). Fructose is best obtained by the hydrolysis of *inulin*, a polysaccharide found in the tubers of dahlias and Jerusalem artichokes.

Fructose is known in both the α - and β -pyranose forms, the ordinary compound being the β -isomer. It passes into furanose forms more readily than glucose and occurs in this way in sucrose.

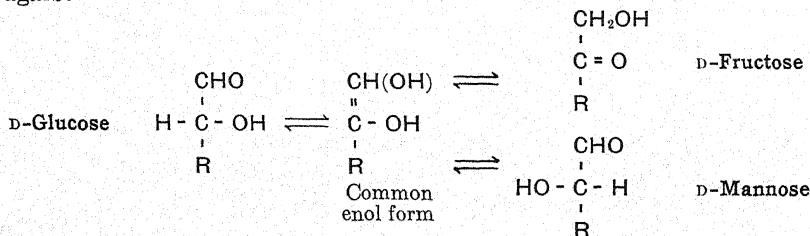


18-12 Mutual Relationships. D-Glucose, D-fructose, and D-mannose give the same osazone. Inspection of their projection formulas (above) shows that all three have identical structures below the dotted line (that is, with respect to carbon atoms 3, 4, 5, and 6). Their differences are with respect to C^1 and C^2 . In the reaction with phenylhydrazine, identical groups become attached to C^1 and C^2 in each sugar, giving

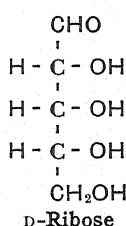
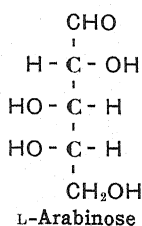
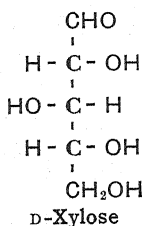


Hence the osazone obtained from each has the same structure throughout.

Interconversions. If a solution of D-glucose, or D-fructose, or D-mannose is allowed to stand in the presence of very dilute alkali, *e.g.*, 0.05 *N* calcium hydroxide, an equilibrium mixture of all three results (the *Lobry de Bruyn transformation*). This is probably due to the formation of a common *enol* form (Sec. 20-13) which can revert to any one of the three sugars:



18-13 Pentoses are, in general, of much less importance than the hexoses. The three that occur most frequently have the following configurations:

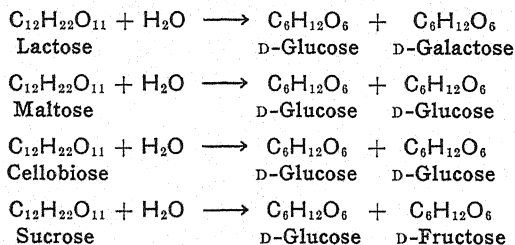


One product of hydrolysis of yeast nucleic acid is β -D-ribofuranose, and thymus nucleic acid yields the corresponding form of 2-desoxyribose.¹ Arabinose and xylose result from the hydrolysis of pentosans.

Pentosans are polysaccharides analogous to starch but yielding mainly pentose sugars. One of the commonest is *xylan*, which consists of D-xylose molecules united like the glucose units of starch. Xylan is found in that portion of the hemicellulose of wood which is soluble in alkalis (wood gum). It is abundant also in corncoobs, oat hulls, and similar plant products. These yield xylose on hydrolysis with dilute sulfuric acid, but their most important use is in the manufacture of *furfural* (Sec. 26-10) by digesting with steam and acid.

DISACCHARIDES

18-14 Disaccharides are sugars which, on hydrolysis, yield two molecules of simple sugars. The four of chief interest are isomers of the composition $\text{C}_{12}\text{H}_{22}\text{O}_{11}$, which yield the following products by hydrolysis:



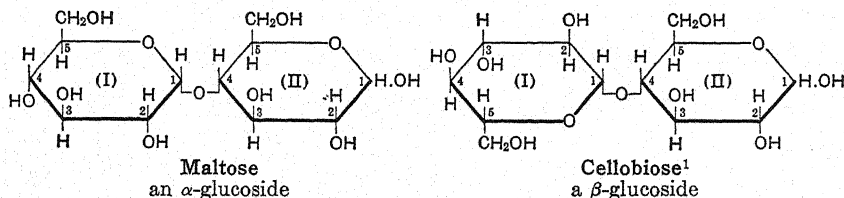
The disaccharides resemble the simple sugars in their solubility relations and other physical properties. All are readily hydrolyzed by acids (sucrose most rapidly) while enzymes show a selective action; maltose is hydrolyzed by *maltase*, sucrose by *invertase*, and cellobiose and lactose by *emulsin*. They are not fermentable, as such, by yeasts; but the latter may furnish also the enzyme necessary for hydrolyzing to fermentable monosaccharides. All form octaacetates, showing the presence of eight hydroxyl groups. Lactose, maltose, and cellobiose (the *reducing* disaccharides) closely resemble glucose in their other chemical properties; they

¹ *Desoxy* sugars are compounds in which one or more H.C.OH groups have lost an oxygen atom and been converted into CH₂.

are fragmented by alkalis, reduce Fehling's solution, form osazones, exhibit mutarotation, and form glycosidic derivatives. Sucrose differs in all these properties.

18-15 Maltose and Cellobiose. Maltose or malt sugar is best obtained by hydrolyzing starch with the aid of the enzyme *diastase*, as explained in connection with the manufacture of ethyl alcohol by fermentation. Cellobiose is the disaccharide obtained by the more difficult hydrolysis of cellulose. Ordinary crystalline maltose (a monohydrate) has a specific rotation of $+111.7^\circ$, which increases on standing to an equilibrium value of $+130.4^\circ$. For cellobiose, $\alpha_D = +14^\circ$ initially and the equilibrium value is $+35^\circ$. The chief difference between the two compounds is found in the selective action of enzymes. Maltose resembles methyl α -D-glucoside in being hydrolyzed by maltase but not by emulsin; cellobiose is hydrolyzed by emulsin but not by maltase and thus resembles methyl β -D-glucoside.

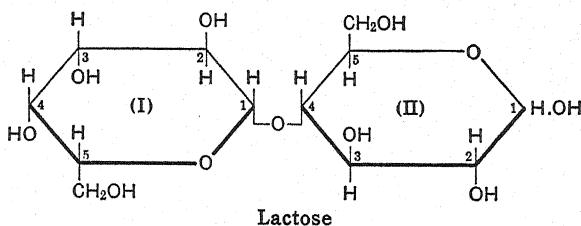
These facts—and much other evidence—lead to the conclusion that maltose and cellobiose are *glucosides* in which a second molecule of glucose corresponds to **R** of the type formulas shown in Section 18.9. The two glucose residues are joined by 1,4-glucosidic linkages—the *alpha* type in maltose and the *beta* in cellobiose:



The glucose residue represented by (I) in these formulas has no aldehyde group either actual or potential. Residue (II), however, has a potential aldehyde group at C¹; through it, maltose and cellobiose resemble glucose in fragmentation by alkalis, reduction of Fehling's solution, formation of osazones, and mutarotation.

18-16 Lactose, or milk sugar, is formed in the mammary glands and occurs in the milk of all animals but has not been found in plant products. Human milk contains about 6 per cent and cow's milk about 4 per cent. It is manufactured by evaporating skim milk and purifying by recrystallization. It is the least soluble and least sweet of the common sugars. Lactose is a β -D-galactoside, represented by the following structural formula in which (I) is a galactose and (II) a glucose residue:

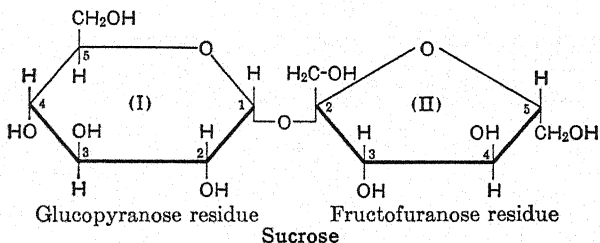
¹ Residue (I) in the cellobiose formula has been inverted in order to maintain true relative positions without making the formula too cumbersome.



18-17 Sucrose, $C_{12}H_{22}O_{11}$, is ordinary table sugar. It is often described as *cane sugar* or *beet sugar*, according to its origin, but the pure product from both plants is identical.

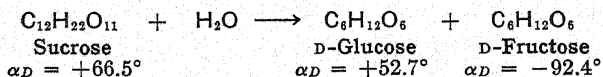
The presence of eight hydroxyl groups in the molecule is shown by the formation of an octamethyl ether and an octaacetate. It forms saccharates of the type $C_{12}H_{21}O_{11}M$ with sodium and potassium hydroxides and more complex saccharates with the hydroxides of calcium, barium, and strontium.

Sucrose differs from the other common disaccharides in that it is quite stable toward alkalis, is nonreducing, does not react with phenylhydrazine, does not exhibit mutarotation, and does not yield glycosidic derivatives. These properties show that *the sucrose molecule contains no carbonyl group, either actual or potential*. The established formula



accounts for this by showing that the glucosidic linkage in sucrose is established between the OH on C^1 of the glucose unit and that on C^2 of the fructose. These are the groups which, in the two hexoses, are responsible for reducing action, mutarotation, etc. In the sucrose molecule both are "blocked" and neither half can change to an open-chain form. The formula also indicates the established fact that the fructose unit in sucrose has the furanose ring.

Inversion of Sucrose. Dilute acids and the enzyme *sucrase* readily hydrolyze sucrose:



This is commonly called the *inversion* of sucrose; because of the strong

levorotation of fructose, the initially dextrorotatory solution of sucrose rotates to the left when hydrolysis is complete; that is, *the sign of rotation is inverted*. The resulting mixture of glucose and fructose is called *invert sugar*. Honey consists largely of invert sugar.

POLYSACCHARIDES

Cellulose and starch are the major products of plant life. Both are high-condensation polymers of D-glucose, into which they are converted on complete hydrolysis. Each corresponds in composition to the formula $(C_6H_{10}O_5)_n$, in which n is a large number which varies within wide limits. In other words, neither cellulose nor starch is a chemical individual in the sense that sucrose is; each is a naturally occurring assortment of similar molecules. Because of their high molecular complexity, these polysaccharides differ from the sugars in solubility relations and in most other physical properties (*e.g.*, they are tasteless instead of being sweet) and in their lower chemical reactivity.

18-18 Cellulose occurs as slender fibers of varying length in the walls of inactive plant cells such as those of trunks, stalks, and stems, of which it often makes up 50 per cent. Thus it is the chief *structural* material of plants. Enormous quantities of *paper* are manufactured from wood fibers (0.15 to 2 mm in length) obtained by heating chips with chemical solutions which dissolve out all gums and other noncellulosic material. The resulting *wood pulp* is thoroughly washed, bleached with chlorine, and mixed with any desired fillers (chalk, talc), sizes (rosin, casein, starch), and dyestuffs. This mixture, suspended in much water, is fed to paper-making machines where the fibers are felted into a continuous sheet which is pressed between rollers and finally dried. The very low tensile strength of wet newsprint testifies to the shortness of the wood fibers of which it is made.

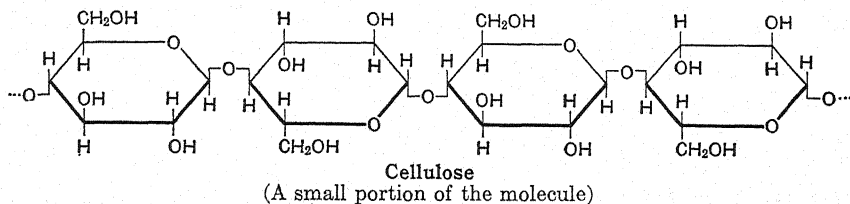
The seed hairs of the cotton boll are almost pure cellulose. The longer ones, usually $\frac{1}{2}$ to 1 inch, are twisted together ("spun") into continuous yarn of the desired thickness and then woven or knitted into fabrics. This *cotton-textile* industry is the world's major source of clothing and of cloth for other purposes. Any cotton textile can be raveled and the threads untwisted to reveal the original fibers as they came from the cotton boll. The bleaching and other treatments which are part of the manufacturing process are possible here—as in the paper industry—because of the chemical inertness of cellulose.

Other industrial sources of cellulose include the bast fibers of flax (which yield linen) and hemp, jute, and sisal, which are used for twine, rope, sacking, etc.

Pure cellulose is obtained most readily from cotton fibers. These

analyze better than 90 per cent of α -cellulose,¹ most of the remainder being water; traces of impurities are removed by treating with fat solvents and dilute alkali. Wood cellulose is more difficult to separate from various hemicelluloses, lignin (a noncarbohydrate), gums, and resins with which it is associated in nature. A good grade of filter paper is substantially pure cellulose.

18.19 Structure of Cellulose. Complete hydrolysis of cellulose by acids yields D-glucose exclusively. Intermediate products of hydrolysis which have been identified include *cellobiose*, other glycosides containing three, four, and six glucose units, and more complicated ones called cello-dextrins. This and all the other available evidence leads to the conclusion that *cellulose consists of a long regular chain of glucose units joined in β -glucosidic linkages at carbon 4*. This is indicated in the following formula and may be crudely visualized by thinking of a very long string, of paper clips:



The average molecular weight of cellulose obtained by physical methods² is of the order of 300,000 to 500,000, corresponding to the union of 2000 to 3000 D-glucose molecules (but some determinations give values indicating as many as 9000 to 11,000 glucose units). X-ray studies on native cellulose fibers show a repeating unit with the interval 10.28 Å, which corresponds well with the calculated length of a cellobiose unit. X-ray diffraction photographs likewise disclose a nearcrystalline regularity in the structure of cellulose fibers; this is especially marked in the very strong fibers of linen and ramie, less so in cotton.

Fibers and Molecules. All visible cellulose fibers are long and slim; *e.g.*,

¹ The material insoluble in 17.5 per cent sodium hydroxide solution at room temperature is called α -cellulose. The "alpha" has no connection with the use of this Greek letter in naming glycosides.

² Ordinary methods for determining molecular weights are useless for giant molecules such as those of cellulose, starch, and proteins. The methods actually used are based on the measurement of osmotic pressures (valid only for substances of very high purity), viscosity, and rate of settling in the ultracentrifuge. The results obtained by these methods are seldom very close together, but all lead to large values. The ultracentrifuge, which gives fields of force up to 500,000 times the force of gravity, is especially useful because it shows when a supposedly homogeneous material is actually composed of molecules of different sizes.

a 1-inch cotton hair is about 1400 times as long as it is wide. They are composed of long, slim molecules—too *slim* to be visible even under the microscope, though they are probably long enough. These molecules are arranged roughly parallel to each other and to the length of the fiber, and adjacent molecules are held together quite firmly by many hydrogen bonds between their polar OH groups. The more nearly parallel the molecules, the more numerous the hydrogen bonds. This submicroscopic structure is responsible for the tensile strength of cellulose fibers, for their insolubility in water and organic solvents, for the fact that cellulose cannot be melted, and for its ability to resist the action of many chemical reagents.

18-20 Chemical Properties. Cellulose is relatively stable toward dilute alkalis and has almost no reducing action. It can be hydrolyzed to D-glucose by acid catalysis, but the action is slow; much effort has been expended in seeking an economical method for hydrolyzing sawdust and other wood waste to fermentable sugar for producing ethyl alcohol. Cellulose is not hydrolyzed by any of the enzymes found in yeast or in man's digestive tract, and therefore cannot serve as human food.¹ It gives no color with iodine (distinction from starch). The importance of the low reactivity of cellulose in the manufacture and uses of paper and cotton textiles has already been mentioned. The mechanical uses of wood and the structural function of cellulose in plants likewise reflect its chemical inertness.

Useful Reactions. Cellulose contains three OH groups for each glucose unit. Its important chemical uses are all based on the formation of *esters*—and, to a less extent, of *ethers*—by reactions at these groups. Some of the major industrial applications are described below. In considering them it is important to bear in mind that the indicated reactions are always accompanied by some cleavages of cellulose chains (“degradation of cellulose”). The products consist of molecules in which the average number of glucose units has been reduced to some 300 to 500. The particular value varies with the nature of the reaction and with the operating conditions, which are usually adjusted to keep the number as large as possible.

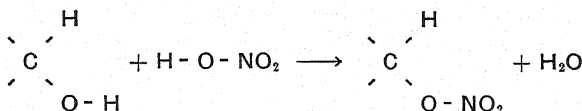
18-21 Cellulose nitrates are manufactured by dipping well-purified cotton linters² or wood pulp into a large excess of a mixture of nitric and

¹ The digestive tracts of herbivorous animals house bacteria which are able to produce sugars from the softer forms of cellulose (hemicelluloses) contained in grass, hay, etc. Hydrolysis by enzymes secreted by microorganisms is doubtless an important step in the *decay* of cellulosic material which takes place in nature on such a huge scale.

² *Linters* are the very short fibers left adhering to cottonseed after the longer, textile fibers have been removed by ginning.

sulfuric acids maintained at 30°C. After 15 to 30 minutes, the charge is dropped into a centrifuge where most of the excess acid is removed. The nitrated cotton is beaten with water and boiled with several changes of dilute alkali to remove the last traces of acid; finally, the remaining water is displaced by ethyl alcohol. The product is a white fibrous material which in appearance closely resembles the original cotton. For safety it is packed into closed containers while still moist with alcohol.

Showing only a single hydroxyl group of cellulose, the essential reaction in nitration is



This yields a *nitric acid ester* of cellulose, as indicated by the name cellulose nitrate. In industry, however, the products of nitration are usually called *nitrocellulose*, like the comparable nitroglycerin.

The properties and uses of nitrated cellulose depend mainly on the extent of nitration. This is controlled by the composition of the mixed acid and is judged by the percentage of nitrogen in the product (Table 18-1). Complete nitration (14.14 per cent N) is hard to attain, and 13.75 per cent nitrogen is said to be the highest produced commercially. The more highly nitrated products, usually known as *guncotton* (13.2 per cent N) and *pyrocotton* (12.6 per cent N), are used for the manufacture of explosives. Those of lower nitrogen content (pyroxylin) go into lacquers and plastics.

TABLE 18-1 COMPOSITION OF NITRATED CELLULOSE
Average Number of OH
Groups Esterified by HNO₃

Per Cent of Nitrogen	Average Number of OH Groups Esterified by HNO ₃
14.14	12 out of 12
13.47	11 out of 12
12.75	10 out of 12
11.96	9 out of 12
11.11	8 out of 12
9.15	6 out of 12

The basis of reference, 12, is the number of hydroxyl groups present in 4 glucose residues of the cellulose chain and corresponds to 24 carbon atoms.

18-22 Nitrocellulose Explosives. Pyrocotton is the raw material used in manufacturing substantially all modern propellants ("smokeless powders") both military and sporting. The rate of detonation is a function of the total *surface* and is so rapid in fluffy, fibrous pyrocotton that this acts as a *brisant* (Sec. 16-13) and is useless as a propellant. For practical use, the surface area and rate of detonation are reduced by colloidizing. Pyrocotton is beaten with a mixture of alcohol and ether to form a plastic

mass. This is forced through a die of suitable diameter and construction and extruded as a continuous, perforated,¹ cylindrical rod. The rods are chopped into pieces of the desired length, and the resulting "grains" are cured by keeping them in a warm, ventilated room until all ether and alcohol have evaporated. During the colloidizing process a stabilizer is added (usually about 1 per cent of urea or diphenylamine); its function is to react with the oxides of nitrogen which are slowly evolved during the storage of all nitrocellulose products; if not removed these render the powder more unstable and its ballistic performance unpredictable. In "double-base" powders, pyrocotton or guncotton is colloidized with nitroglycerin (5 to 60 per cent).

Propellants are explosives designed to expel a projectile—birdshot, a bullet, a 16-inch shell—from some kind of "gun" with the momentum needed to reach its objective. Such an explosive must build up pressure somewhat gradually to move the projectile from its resting state and give it the necessary muzzle velocity. If the rate of detonation is too great, the gun may be shattered; or, in military use, the high explosive of the shell may be set off. Gelatinized nitrocellulose is superior to all other explosives as a propellant because its rate of detonation is subject to accurate control—in part, by choosing between single- and double-base powders, but mainly by suitable variations in the surface area of the explosive charge (Table 18-2).

TABLE 18-2 PROPELLANT EXPLOSIVES
Relation between weight of projectile, charge of explosive, and burning area.

	Projectile	
	3-inch shell	16-inch shell
Length of powder grain (inches).....	0.6	2.3
Diameter of powder grain (inches).....	0.25	1
Grains per pound.....	668	9.5
Burning surface (sq. in. per lb.).....	580	123
Weight of projectile (pounds).....	13	2400
Weight of propellant (pounds).....	5	840

A double-base powder containing 50 parts each of nitrocellulose and nitroglycerin (in a standard grain) develops its maximum pressure of 31,000 psi in 0.0185 second or at the rate of 1,700,000 pounds per second. A powder of the same granulation containing 75 per cent nitrocellulose and 25 per cent nitroglycerin attains a maximum pressure of 35,000 psi but requires 0.032 second (a rate of 1,100,000 pounds per second). For a single-base nitrocellulose powder, the rate is about one-fifth that of a 50:50 double-base propellant.

¹ The die leaves seven narrow, cylindrical openings running lengthwise of the grain. As surface decomposition proceeds, these openings grow in diameter; thus the total surface and consequent rate of reaction *increase* with time.

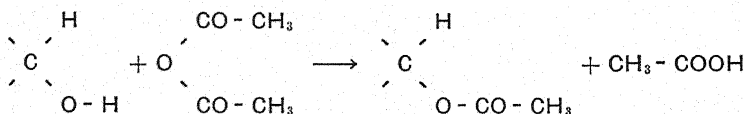
18-23 Pyroxylin lacquers and plastics are made from nitrocellulose containing about 10.8 to 11.6 per cent N, commonly called pyroxylin. This material is highly inflammable but nonexplosive. *Lacquers* (Duco, Zapon, etc.) are made by dissolving pyroxylin in a mixture of organic solvents of suitable volatility (butyl and amyl acetates, Cellosolve, etc.) and adding a plasticizer and a suitable pigment or dye. They are usually applied with a spray gun, though brush lacquers are also available. *Drying* consists in the evaporation of the solvent (cf. paint, Sec. 16-24), which leaves an adherent film of pyroxylin colored by the dye or pigment and rendered elastic by the plasticizer. Such lacquers are now used in large quantities to replace paint and varnish for coating metals, especially automobiles, and interior woodwork and furniture. A small amount of a plasticizer is necessary to give the film elasticity and to prevent shrinkage and wrinkling (cf. Sec. 24-11).

Pyroxylin plastics (Celluloid, Pyralin, etc.) are made by colloiding pyroxylin cotton with relatively large amounts of a plasticizer such as camphor. High inflammability is a disadvantage which has led to their replacement by other plastics for many purposes. The older type of cinema and X-ray film is an example.

Collodion is a 4 per cent dispersion of pyroxylin in a mixture of alcohol and ether; *flexible collodion* contains also small amounts of camphor and castor oil.

Artificial leather can be made by coating a cotton fabric with a solution of pyroxylin in ethyl acetate, carrying a suitable dye or pigment and a plasticizer. Before it is quite dry, it is customary to impart the "grain" of a real leather by passing under a metal roll on which the skin markings of some animal have been reproduced by electroplating (Fabrikoid). Other plastic materials such as ethyl cellulose may be used instead of pyroxylin.

18-24 Cellulose acetate is manufactured by treating purified linters or wood pulp with a cold mixture of acetic anhydride, glacial acetic acid, and a little sulfuric acid. The essential reaction is



Acetylation cannot be regulated, and the product is fully acetylated cellulose in which substantially all hydroxyl groups have been esterified. When washed and dried, this cellulose triacetate is a white brittle substance resembling in appearance dried shredded coconut; it is insoluble in acetone and most other solvents except chlorinated hydrocarbons, has little tensile strength, and is of practically no use as such. In industrial practice it is partially hydrolyzed by boiling with dilute acid until only

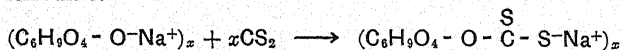
about 10 out of 12 hydroxyl groups remain acetylated.¹ After washing and drying, this thermoplastic material is ready for the manufacture of acetate rayon (Sec. 18-27) and plastics.

Photographic film of low inflammability is made by dissolving cellulose acetate in a suitable solvent and casting the clear solution on to the broad, smoothly finished rim of a huge wheel; this revolves slowly in a counter-current of air which evaporates the solvent and leaves a film strong enough to be stripped off before the wheel has completed a revolution. Other thin films are used for wrappings and thicker ones for making transparent containers. Plasticized cellulose acetate may be cast in blocks from which rigid sheets are sawed for fabrication into lamp shades, "windows" for various purposes, spectacle frames, etc. Solutions of cellulose acetate in suitable organic solvents are used for surface coatings, including the impregnation of documents for permanent preservation.

Cellulose acetate molding powders are made by incorporating plasticizers, *e.g.*, diethylphthalate, with flake acetate; usually a dye is added and often an opaque substance; the mass is then chopped to grains and dried. Industrial powders (Lumarith, Tenite, etc.) are molded—by injection, extrusion, or compression—into a wide variety of consumer items for both practical and ornamental use.

Cellulose propionate and mixed esters—the acetate-propionate and the acetate-butyrate—are produced similarly to the acetate, though on a smaller scale, and are used for molding.

18-25 Cellulose Xanthate; Viscose. The raw material for this industry is purified wood pulp in the form of sheets resembling high-grade blotting paper. These are soaked in a cold 17.5 per cent solution of sodium hydroxide for further purification and for the formation of *alkali cellulose*. The latter is a cellulose salt or alcoholate in which the OH hydrogen of C² in most of the glucose units has been replaced by sodium. Excess liquid is pressed out and the moist alkali cellulose shredded and aged at room temperature for two or three days. It is then churned with carbon disulfide, through which it is converted into red-brown *cellulose xanthate* or its sodium salt:



When this granular solid is treated with dilute sodium hydroxide, it yields a yellow, highly viscous colloidal solution called *viscose*. After aging several days—during which time the viscosity decreases through

¹ The formula for a single unit of cellulose triacetate may be written $\text{C}_6\text{H}_4\text{O}_2 \cdot 3\text{C}_2\text{H}_3\text{O}_2$ (formula weight 288), from which a content of 62.5 per cent of acetic acid is calculated. The degree of acetylation is usually reported in terms of "combined acetic acid," which runs about 54 to 55 per cent in the material used for making rayon and a little higher for plastics.

complicated reactions which are not well understood—the “ripened” viscose is filtered by pressure and used for the manufacture of rayon (Sec. 18-27) and cellophane.¹

Cellophane is manufactured by feeding viscose through an adjustable, very narrow slit into an acid solution. Acid quickly hydrolyzes the xanthate and precipitates *regenerated cellulose* as a continuous transparent sheet about 50 inches wide. This passes through a series of baths in which it is washed, bleached, softened by absorption of glycerol, air-dried, and wound into rolls. Regenerated cellulose gives the same analysis as native cellulose, but the average size of the molecule has been reduced to 350 to 400 glucose units and the molecules have little orderly arrangement. Films of it are quite permeable by water and water-soluble gases. Most cellophane is given a further, moistureproofing treatment in which the sheets are coated with a very thin layer of plasticized pyroxylin. Viscose sausage casings are made as continuous, seamless tubes by extrusion through a circular slit.

18-26 Rayon is the group name for all man-made fibers with a cellulose base.² The fundamental principle is the same in the various methods: the short natural fibers of cotton linters or wood pulp are brought into colloidal solution through a chemical reaction, and the solution is used to produce *continuous* filaments which are practically endless. However prepared, the carefully filtered “spinning” solution is forced through a *spinneret*—a metal disk containing 15 to 60 holes, which are often as small as 0.03 mm in diameter. A filament is produced from each hole, by an appropriate physical or chemical change which varies with the process. All the filaments from a spinneret are collected in a single strand, twisted somewhat to hold them together, and the yarn thus formed is wound on a spool or spindle for shipment to textile manufacturers.

Most rayons have a high luster which is often removed by introducing a finely divided solid, such as titanium dioxide, into the spinning solutions. Dyes are added occasionally. Much of the continuous filament produced is chopped into lengths of a few inches—*staple fiber*—which are spun together like cotton or wool. This gives fabrics with the rougher finishes desired for some classes of goods. Filament and staple rayon yarns are woven or knit into fabrics either alone or in combination with one another or with cotton, wool, nylon, etc.

¹ An interesting minor use is the manufacture of cellulose *sponges*. Ripened viscose is stirred with shredded vegetable fibers and crystals of hydrated sodium sulfate. The mass is poured into molds and the viscose coagulated to regenerated cellulose. The sodium sulfate is then dissolved out with water, leaving large or small holes according to the size of the crystals used.

² This definition excludes deliberately the all-synthetic fibers such as nylon, Dacron, Vignol, Dynel, etc.

Denier. Continuous filaments and the yarns made from them are rated by denier, which is *the weight in grams of 9000 meters*. The worm-silk filament is about 1.2 denier; thus a strand made by twisting 10 of them together would be about 12 denier. Rayon yarn for textiles is made principally in 75 to 150 deniers, controlled by the number and size of the spinneret holes. Maximum flexibility and softness for a given denier yarn is attained with a large number of very fine filaments.

18-27 *Viscose rayon* is made by forcing ripened viscose through a spinneret into an acid solution, thus producing filaments of regenerated cellulose. These are collected into strands of yarn, washed, dried, and wound. The lack of orderly molecular arrangement in regenerated cellulose gives viscose rayon a somewhat lower tensile strength than cotton, especially when wet. Conversely, dyes are able to penetrate and affix themselves more readily.

A large amount of high-tenacity¹ viscose rayon (Cordura, etc.) is produced in deniers around 1600 for making cords in tires, fabrics for heavy-duty parachutes, etc. The essential difference in manufacture is that the freshly formed, wet filaments are greatly stretched. This brings about a much better alignment of the molecules, which is reflected in the greater strength of the finished yarn. Fortisan is an exceptionally high-tenacity fiber of regenerated cellulose; it is made by hydrolyzing off the acetyl groups of cellulose acetate while the filaments are being stretched.

Cellulose acetate rayon (Celanese, Acele, etc.) is produced by forcing an acetone solution of cellulose acetate through a spinneret. A current of hot air on the other side evaporates the acetone, and continuous filaments of cellulose acetate are formed and collected as yarn. Having relatively few OH groups, cellulose acetate rayon takes up less moisture than viscose and has a lower affinity for dyestuffs (Sec. 25-22). It lends itself well to the production of fine-filament, low-denier yarns suitable for luxury fabrics (velvets, crepes, etc.).

Cupriammonium rayon (Bemberg) is made by treating cellulose fibers with an ammoniacal solution of cupric oxide, which dissolves them through limited hydrolysis and complex-formation. The filtered solution is spun through a spinneret with relatively large holes (0.25 to 0.75 mm) into a coagulating bath which produces filaments of regenerated cellulose. The wet filaments are highly stretched—down to an average denier of 1, or as low as 0.4 for special purposes. These fine filaments, which have a luster like that of worm silk and a tenacity somewhat higher

¹ The tenacity, or strength, of yarns is usually measured in *grams per denier*. Thus if a load of 150 grams is just enough to break a 75-denier yarn, the tenacity is 2 grams per denier. This is about the average value for ordinary viscose rayon (as compared with 2.5 to 3 for cotton and 5.5 to 6 for linen). Some high-tenacity viscose rayons will support up to 7 grams per denier.

than other rayons, are used in making very thin (sheer) fabrics. The production is relatively small.

TABLE 18-3 NATURAL AND ARTIFICIAL FIBERS; 1950

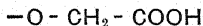
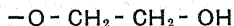
	Pounds
Rayon production—world.....	3,500,000,000
Rayon production—USA.....	1,260,000,000
Textile fiber consumption, USA	
Cotton.....	4,720,000,000
Rayon.....	1,254,000,000
Wool.....	605,000,000
Silk.....	8,400,000
Synthetic fibers (nylon, etc.).....	145,000,000
Rayon distribution, USA	
Viscose.....	817,700,000
Filament yarn for textiles†.....	320,600,000
High-tenacity yarn for tires, etc.....	307,700,000
Staple.....	189,400,000
Acetate.....	435,900,000
Filament yarn for textiles.....	320,800,000
Staple.....	115,100,000

† Includes the relatively small amount of cupriammonium rayon.

18-28 Cellulose Ethers. Ethyl cellulose (Ethocel) is the principal product of this type. It is manufactured by treating alkali cellulose (Sec. 18-25) with ethyl chloride or ethyl sulfate. Ether linkages are thus formed by the Williamson reaction. The usual product corresponds to the ethylation of about 2.4 to 2.5 hydroxyl groups per glucose unit; the latter range from 200 to 500 per molecule. Ethyl cellulose is superior to either the acetate or nitrate for certain types of coating compounds and moldings.

The methyl and other cellulose ethers containing only about 1 to 1.5 alkyl groups per glucose unit are soluble in water. Threads made from them are sometimes woven into cloth and later dissolved out to produce open-work patterns.

Hydroxyethyl cellulose (Cellosize) can be made by treating cellulose with ethylene oxide, or alkali cellulose with ethylene chlorohydrin. Carboxymethyl cellulose is made by reaction between alkali cellulose and sodium chloroacetate. Thus these ethers contain the following groups, respectively, attached to carbon atoms of the glucose rings:



Water-soluble forms of both are known and are used in textile finishing.

18-29 Starch is the form in which most plants store carbohydrate in seeds or tubers as reserve food for their embryos. Native starch occurs in granules of characteristic sizes, shapes, and striations, by means of which their origin can be recognized through microscopic examination. These granules are quite insoluble in cold water and all ordinary solvents. When heated with water at about 55°C, the granules swell to relatively enormous size and finally disappear to form gelatinous starch paste.

Dilute starch paste will pass through ordinary filter paper but not through semipermeable membranes. On account of its physical properties, large quantities of starch are used in laundries, in sizing paper and textiles, and in the preparation of wallpaper paste and other adhesives. Its most important use is as *food*. Starch is readily recognized by the intense blue color imparted by a trace of iodine. Like cellulose, it has little reducing action and is resistant to alkalis. It is hydrolyzed by acids and by enzymes, through maltose, to D-glucose. The fact that maltose is an intermediate in enzymotic hydrolysis is an indication that the glucose units in starch are bound by α -glucosidic linkages, in contrast with the β linkages of cellulose.

Starch from any source can be separated with the aid of water and alcohols into two components called *amylose* and *amylopectin*.¹ Ordinary corn and potato starches contain about 22 per cent *amylose*. This is the component which gives the deep blue color with iodine and the one more readily hydrolyzed by starch-splitting enzymes (amylases). Amylose molecules are composed of long, unbranched chains similar to those of cellulose except that they are shorter and the units are joined by *alpha*-glucosidic 1,4 linkages. One study in the ultracentrifuge indicates that the amylose from cornstarch contains molecules ranging in molecular weight from 17,000 to 225,000 with half of them in the 31,000 to 61,000 range. The last figures correspond to about 200 to 400 D-glucose residues per molecule.

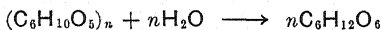
Amylopectins give red to purple colors with iodine. Most methods indicate molecular weights of the order of 200,000 to 300,000, but values up to a million have been reported. There is little doubt that amylopectin molecules are quite highly *branched*² and contain a repeating unit of 24 to 30 glucose residues. One interpretation (that of Staudinger) is that the molecules contain a long fundamental chain with branches joined on at regular intervals by α -1,6-glucosidic linkages. There are indications from X-ray studies that amylose molecules are wound in spirals—an arrangement which would be favored by *alpha*-glucosidic linkages. Certainly, branched molecules cannot be closely aligned, and there are few opportunities for hydrogen bonding between them. These differences may explain why starch forms colloidal dispersions in water while cellulose is entirely insoluble.

¹ These terms will be used here in the sense proposed by K. H. Meyer (1940). Usage in the older carbohydrate literature is confusing; "amylose" often refers to the material leached from starch granules by hot water.

² The *end* group of a main chain and of each branched chain must contain a glucose residue with *four* OH groups, as in residue (I) of the formula for maltose on page 352. The number of these end groups and, therefore, the degree of branching, can be determined approximately by existing chemical methods.

18-30 Hydrolysis of starch is its most important chemical reaction. Large quantities of crystallized corn sugar (D-glucose) and corn syrup are manufactured by hydrolyzing cornstarch with steam and dilute acid. In the manufacture of ethyl alcohol and alcoholic beverages from grain and other starchy materials, it is hydrolyzed to maltose by diastase. And in performing its great function as food for man and animals, starch is hydrolyzed to glucose through catalysis by the enzymes of the digestive tract.

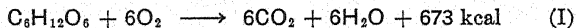
The over-all equation for the complete hydrolysis of starch



is a summation of many intermediate steps. Various molecules of decreasing complexity (dextrins), as well as maltose, are intermediate products. *Dextrins* of varying properties are manufactured from starch by enzyme, acid, heat, and oxidation treatments. They are used widely as adhesives (*e.g.*, on postage stamps and envelope flaps), in sizing paper and textiles, etc.

18-31 Carbohydrate Food. The largest single item in the food of man and grain-fattened animals is starch. The mention of such widely used starch foods as bread, rice, potatoes, and cereal breakfast dishes suffices to establish this position of starch in human diet. "Prepared" starch, *i.e.*, starch separated from the noncarbohydrates with which it occurs in grains, is also used in many food products such as ice cream, confectionery, cocoa, chocolate, and sausages. Sucrose is also an important item of food, especially in the United States where the annual consumption of refined cane and beet sugar averages more than a hundred pounds per person. Milk sugar (lactose) is a third source of carbohydrate in the diet.

Starch, sucrose, and lactose are hydrolyzed in the digestive tract to monosaccharides. These are absorbed through the intestinal wall into the blood, by which they are transported throughout the body. The many and involved chemical reactions which follow in biological oxidation (Sec. 27-16) may be summarized for present purposes by the over-all equation



The energy thus made available from the carbohydrate foodstuffs is the principal source of animal energy. Part of it can be utilized for muscular activity; the larger part is radiated as body heat.

Glycogen. One stage in the utilization of carbohydrate food is the conversion of glucose and the other monosaccharides into glycogen for temporary storage, chiefly in the muscles and liver. Glycogen forms opalescent, colloidal solutions in cold water and gives violet to brown colors

with iodine. It is a D-glucose polymer, $(C_6H_{10}O_5)_n$, in which the units are joined by α -glucosidic linkages in a structure similar to that of starch amylopectin but even more highly branched. Molecular-weight determinations lead to values of one to several millions.

18-32 Carbon Cycle; Photosynthesis. The average human adult exhales 1.5 to 2 pounds of carbon dioxide per day. This is derived from oxidation of the food, in which carbohydrates predominate, by oxygen withdrawn from the atmosphere. In the same way, when fuels (wood, coal, natural gas, and petroleum products) are burned for the production of energy, the oxygen of the air is depleted and carbon dioxide is increased. The total amount of CO_2 discharged into the air from lungs, factory chimneys, and automobile exhaust pipes is measured in millions of tons daily. The decay of huge quantities of vegetation makes a further large contribution. Yet the proportions of oxygen and carbon dioxide in the atmosphere remain unchanged year after year. This is largely because the effects of these oxidative processes are reversed in growing *plants*, which withdraw carbon dioxide from the air and replace it by oxygen. At the same time, sugars appear in the plant juices and are later stored as starch or built into cell walls as cellulose. The over-all equation for the synthesis of one mole of D-glucose in a plant



is the exact reverse of (I) of the last section. Together, (I) and (II) constitute the *carbon cycle* of nature.

Photosynthesis. The series of reactions summarized by (II), which proceeds with the absorption of energy as sunlight, constitutes the process of photosynthesis (Gr., *photos*, light). The fundamental steps occur in the green parts of plants, with the aid of the *chlorophyll* which imparts the green color. We still do not know exactly *what* reactions occur, *how*, or *why*; the importance of the problem has long made it the subject of scientific investigation—and current researches hold out promise of at least a partial solution.

It has been estimated that photosynthesis fixes annually 3×10^{11} tons of carbon as carbohydrates. With the exception of water power, all our primary sources of energy go back to this fixation of solar radiation. This is true of current annual crops—sources of the starch and sugar which, in the bodies of man and his domestic animals, yield the energy which they convert into external work. This is true also of our industrial energy sources—coal, natural gas, petroleum—in which solar energy was stored up by photosynthesis in past geological ages. It has been well said that: "To study the carbohydrates is, in brief, to study the great molecular channel through which solar energy flows to us."

Questions

1. Summarize the experimental evidence and the deductions which establish the aldohexose open-chain formula for glucose.
2. In the light of this formula: (a) explain why glucose would be expected to be freely soluble in water; (b) predict how, if at all, water-solubility should be affected by acetylation.
3. Write structural equations for all reactions involved in the formation of an osazone from D-mannose.
4. Explain why the reducing action of glucose on alkaline copper solutions cannot be explained as a simple matter of oxidation of CHO to COOH.
5. Write the projection formulas of several aldohexoses belonging to the D series and those of their mirror-image isomers of the L series.
6. (a) Define and illustrate mutarotation. (b) Explain the mutarotation of the sugars in terms of their cyclic, α and β forms.
7. The configurations about C¹ in α -D-glucose and β -D-glucose are those of the two mirror-image arrangements which are possible about any asymmetric carbon atom. Explain why these two forms of D-glucose do not have equal and opposite rotations.
8. (a) What are glucosides? Glycosides? Aglucons? (b) Show the difference between methyl α -D-glucoside and methyl β -D-glucoside and explain why these compounds are nonreducing and do not exhibit mutarotation.
9. When D-glucose is treated with methanol and HCl, only the OH on C¹ is methylated (formation of a methyl glucoside). The remaining four OH groups can be methylated through reaction with methyl iodide and silver oxide. When this penta-methyl compound is treated with dilute acids, only the OCH₃ group on C¹ is hydrolyzed. Offer an explanation of the higher reactivity at C¹ which is demonstrated by these facts.
10. Explain the structural differences indicated by the terms pyranose and furanose.
11. (a) Describe the essential structural differences between D-glucose, D-mannose, and D-fructose. (b) Explain why these three sugars yield the same osazone.
12. Name the four important disaccharides, write the molecular equation for the hydrolysis of each, and name the products.
13. (a) What is the essential difference in the structures of maltose and cellobiose? (b) In the formulas of these sugars and of lactose, point out the grouping responsible for the fact that they are reducing, form osazones, and exhibit mutarotation. (c) Explain accurately why sucrose lacks these properties.
14. Explain what is meant by the *inversion* of sucrose and how this differs from mutarotation.
15. Name: (a) two sugars which are position isomers; (b) two which are mirror-image isomers; (c) two which are stereo but not mirror-image isomers.
16. (a) What is the role of cellulose in plant economy? (b) What are the principal industrial sources of cellulose fibers? (c) What are the major applications which depend purely upon their *physical* properties?
17. (a) Analysis of the purest cellulose gives the empirical formula C₆H₁₀O₅. Explain how this is possible when the molecule must contain at least one glucose residue with six oxygen to six carbon atoms. (b) Pure cellulose is described as having a *very slight* reducing action. Explain why it should have *any*.
18. The ratio of polar oxygen atoms to carbon in water-insoluble cellulose is not much different from that in freely soluble D-glucose. Suggest two reasons why cellulose is insoluble in water.

19. The tenacity of linen fibers averages at least twice that of cotton. Connect this with the X-ray diffraction patterns which show that the structure of linen is much the more regular.

20. Prepare a chart showing the essential structures and indicating the more important applications of man-made cellulose esters.

21. (a) Contrast the composition, properties, and uses of pyrocotton and pyroxylin. (b) Contrast the requirements for propellants with those for brisants ("high" explosives). (c) Describe the manufacture and use of smokeless powder. (d) What is the difference, other than speed, between the drying of a pyroxylin or a cellulose acetate surface coating and the drying of paint?

22. (a) Dried cotton fibers take up about 11 per cent of their weight of moisture in air of standard humidity. Would you expect the moisture uptake of cellulose acetate yarn to be greater or less than this, and why? (b) Explain the fact that cellulose acetate and pyroxylin are thermoplastics while cotton and wood pulp are not softened by heat.

23. (a) Outline the entire procedures for the manufacture of viscose, acetate, and cupriammonium rayons from wood pulp and/or linters. (b) What is the essential difference, if any, in the chemical composition of garments made from these three kinds of rayon? (c) What is the essential difference in the *physical* make-up of cotton cloth and rayon cloth?

24. (a) Given cotton linters and any desired chemicals, indicate how you would prepare a cellulose acetate-butyrate mixed ester. (b) It is desired to make a plastic object which must be exposed steadily to dilute acids and/or alkalis. Considering the chemical natures of cellulose acetate and ethyl cellulose (and assuming 2.5 hydroxyl groups per glucose unit reacted in each) which would you expect to give longer service and why? (c) Predict the relative solubility in organic solvents of ethyl cellulose and carboxymethyl cellulose.

25. Compare starch and cellulose with respect to physical properties, chemical properties, and molecular structure. What fundamental difference in structure is revealed by the fact that they yield on hydrolysis maltose and cellobiose, respectively?

26. Starch is not fermentable by yeast. Reconcile this statement with the fact that starch serves as a raw material for the biochemical manufacture of ethyl alcohol (Sec. 8-17) and of butanol and acetone (Sec. 8-21).

27. (a) From equation (I), Section 18-31, calculate the heat liberated when 1 gram of glucose is burned completely. (b) How would this value differ for 1 gram of starch? (c) What two factors combine to explain why these calorific values are so much smaller than the 9.4 kcal given by 1 gram of an average fat (cf. Sec. 11-17).

28. Explain the quotation: "Bread is the staff of life."

29. Recalling the principal carbohydrate foods, which monosaccharide will largely predominate in the products of digestion and which others will normally be present there, though in much smaller amounts?

30. Trace each of the following manifestations of energy back to its origin in photosynthesis: (a) the illumination of Times Square; (b) a cruiser or a diesel truck in motion; (c) a 16-inch shell in motion; (d) the explosion of such a shell if filled with TNT (Sec. 24-2); (e) an airplane or automobile in motion; (f) a football in motion following the kickoff.

CHAPTER 19

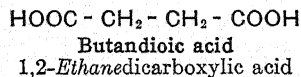
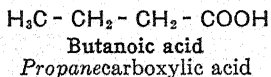
POLYBASIC ACIDS AND THEIR DERIVATIVES

An acid is described as polybasic if it contains more than one ionizable hydrogen atom and is able, therefore, to neutralize two or more equivalents of a base such as sodium hydroxide. The commonest and most important organic compounds of this kind are those containing two carboxyl groups.

19.1 Aliphatic Dicarboxylic Acids. The naturally occurring acids of this type usually have their two COOH groups at the ends of normal, saturated carbon chains. Thus they conform to the type formula $\text{HOOC}(\text{CH}_2)_n\text{COOH}$. These, and others with branched chains, can be prepared by general reactions already studied and illustrated below, or by special methods such as the malonic ester synthesis (Sec. 20.19). Broadly speaking, chemical properties can be predicted quite accurately on the assumption that, under appropriate conditions, either one or both carboxyl groups will react as in the simple fatty acids and give the same types of derivatives. The major exceptions are related to the number of carbon atoms which separate the COOH groups.

The normal dicarboxylic acids are usually called by names given them long ago to suggest the natural source from which they were first obtained. Synthetic acids with forked chains are commonly named as alkyl substitution products of these normal acids, *e.g.*, $(\text{H}_3\text{C})_2\text{C}(\text{COOH})_2$, dimethylmalonic acid.

Systematic Nomenclature. Two methods for naming acids, recognized by the IUC system, may be illustrated as follows:



The preferred names for these four-carbon acids (butanoic and butandioic) regard them as derived from the *corresponding* hydrocarbon, containing the *same* number of carbon atoms—that is, as having been formed from *n*-butane by the oxidation of its CH_3 groups to COOH. These names become less convenient as structures grow more complicated; then it is often preferable to use the other system, in which the COOH group is regarded as a *substituent*.

19.2 Physical Properties. The effects of introducing one COOH group into an organic molecule were shown in Table 11.2, where the

physical properties of acetic acid were compared with those of ethane. These effects are increased by the introduction of a second carboxyl group. All the dicarboxylic acids are nonvolatile, crystalline solids. The lower members, in which the polar COOH groups form a major part of the molecule, are soluble in water but only sparingly so in solvents such as chloroform, ether, and benzene; with increasing length of the carbon chain, these solubility relations are reversed. Successive members containing even and odd numbers of carbon atoms show an alternation in melting points, solubilities, and other physical properties similar to that noted in connection with the fatty acids but even more marked.

Ionization. The number of carbon atoms separating the carboxyl groups has a striking effect on the strength of dicarboxylic acids, as may be seen from the following primary ionization constants:¹

Acid	Formula	$K_{a1} \times 10^5$
Oxalic	HOOC.COOH	6500
Malonic	HOOC.CH ₂ .COOH	160
Succinic	HOOC.CH ₂ .CH ₂ .COOH	8
Glutaric	HOOC.CH ₂ .CH ₂ .CH ₂ .COOH	5
Adipic	HOOC.CH ₂ .CH ₂ .CH ₂ .CH ₂ .COOH	4

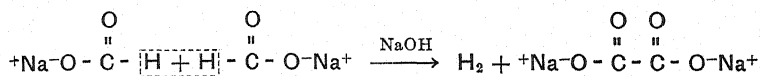
Oxalic acid, in which the COOH groups are joined directly, is one of the strongest of all organic acids; it is more highly ionized than phosphoric, though still much weaker than sulfuric. There is a striking drop on passing to malonic acid, in which the carboxyl groups are separated by CH₂; but malonic acid is about ten times as highly ionized as acetic. With further separation of the COOH groups, ionization drops to the order of magnitude found in the monocarboxylic acids (Table 11.1).

These facts are consistent with what should be expected from the principle of induction. The $+\delta$ charge on the carboxyl carbon makes the COOH group electrophilic. When two of them are directly united, in oxalic acid, each tends to withdraw electrons from the other, thus making it easy for a proton to separate, as hydronium ion, from one of them. The rapid falling off in ionization as CH₂ groups are interposed is consistent with other evidence that inductive effects are relayed very poorly along a saturated carbon chain.

19.3 Oxalic acid, HOOC.COOH, occurs in many plants in the form of its salts, the oxalates. It is formed by the oxidation of ethylene glycol with nitric acid and is also the end product when various other, more complex organic compounds are vigorously oxidized (*e.g.*, sugar, sawdust).

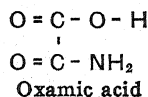
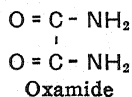
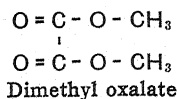
¹ The *primary* ionization of any polybasic acid—that is, the ionization of the first hydrogen atom—is always much higher than for a secondary or further stage.

Oxalic acid is usually manufactured by heating sodium formate with an alkali, which yields sodium oxalate:



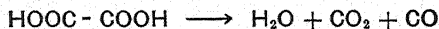
Oxalic acid crystallizes from water solutions as the hydrate, $H_2C_2O_4 \cdot 2H_2O$ (m.p. $101.5^\circ C$), in which form it is sold and used. The hydrate is slowly converted into the anhydrous acid when kept in a dry atmosphere or gently heated. This compound melts with decomposition at 186 to 187° and sublimates at $100^\circ C$. The crystals of the hydrate dissolve in water to the extent of 10 grams per 100 ml at $20^\circ C$.

Oxalic acid forms mono- and diesters and amides and most of the other types of simple and mixed derivatives to be expected from the independent action of its two carboxyl groups, *e.g.*,



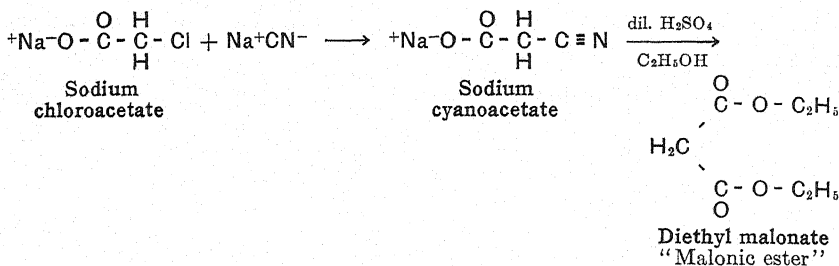
Like other dibasic acids it forms both acid and normal salts such as KHC_2O_4 , $K_2C_2O_4$, CaC_2O_4 , etc. Acid potassium oxalate can be obtained by dividing a solution of oxalic acid in halves, fully neutralizing one portion with potassium hydroxide, and then mixing; on concentration by evaporation, the mono potassium salt crystallizes out because it is the least soluble substance present.

Special Properties. Oxalic acid is the only compound known or possible in which two carboxyl groups are joined directly. Due to this unique structure, some of its properties differ sharply from those of other acids. Its exceptional strength—high degree of ionization—has already been mentioned. Oxalic acid is resistant to nitric acid but differs from all other saturated acids (except formic) in being easily oxidized by permanganate solutions and various other oxidants. This is the origin of the *reducing action* involved in the use of oxalic acid and the oxalates as bleaching agents, ink removers, in photography, and for the standardization of potassium permanganate solutions in quantitative analysis. Oxalic acid does not form an anhydride; dehydration, by heat or sulfuric acid, yields only the oxides of carbon:

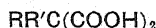


This decomposition is a convenient method for making carbon monoxide in the laboratory.

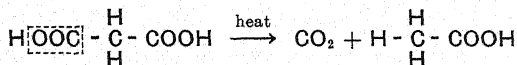
19-4 Malonic acid, $\text{HOOC} \cdot \text{CH}_2 \cdot \text{COOH}$, and its esters are best prepared from chloroacetic acid by the nitrile synthesis. Chloroacetic acid is neutralized with sodium carbonate and then heated with a solution of sodium cyanide to replace Cl by CN; boiling with dilute sulfuric acid hydrolyzes the CN group to COOH, giving malonic acid. The more common procedure is to heat sodium cyanoacetate with ethyl alcohol and sulfuric acid; this effects in one operation the hydrolysis of the nitrile and the esterification of both carboxyl groups:



This diethyl ester of malonic acid is commonly called *malonic ester*. It is an important synthetic reagent in the laboratory and in industry, especially for making various substituted malonic acids (Sec. 20-19) of the types

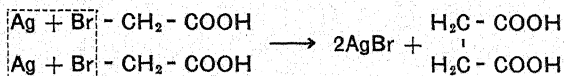


The most unusual property of malonic acid is its ready decarboxylation by heating:

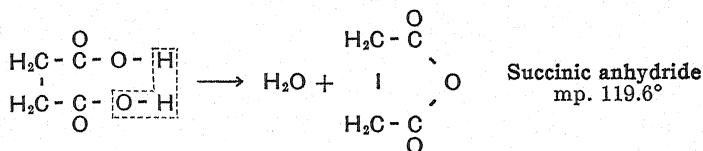


This property is shared by all acids in which *two carboxyl groups are joined to the same carbon atom*—that is, by all substituted malonic acids. The product of each is a monocarboxylic acid containing one less carbon atom.

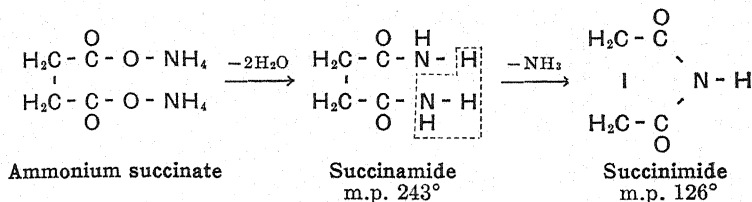
19-5 Succinic acid, $\text{HOOC} \cdot (\text{CH}_2)_2 \cdot \text{COOH}$, was first obtained from amber (L., *succinum*), from which it was named. It can be prepared by such general reactions as heating ethylene dichloride with sodium cyanide and hydrolyzing the resulting succinonitrile, and by heating bromoacetic acid with silver dust (an application of the Wurtz-Fittig principle):



When dry succinic acid is heated, it does not lose CO_2 like malonic acid but, instead, a molecule of water is eliminated between the two carboxyl groups forming a *cyclic* anhydride:

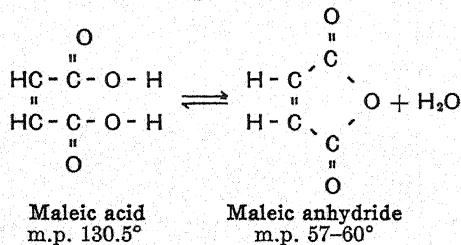


The oxygen atom in the five-membered ring of succinic anhydride can be replaced by nitrogen if the substance is heated in a stream of dry ammonia. The same product, succinimide, is obtained also by strongly heating either ammonium succinate or succinamide:



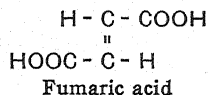
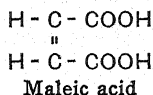
The formation of cyclic anhydrides and cyclic imides is a property characteristic of those acids in which carboxyl groups are separated by *two* or by *three* carbon atoms and is confined to acids of these structures. The use of models shows that these are the ones in which the carboxyl groups can most readily approach each other and thus provide opportunity for interaction and the formation of *five*- and *six*-membered rings. The properties of cyclic anhydrides and imides are considered more fully in connection with phthalic anhydride and phthalimide (Chap. 24), the most important examples. It suffices to mention here that such compounds enter readily into many reactions which involve ring opening, *e.g.*, succinic anhydride reacts like acetic anhydride—though somewhat more slowly—with water, alcohols, phenols, ammonia, and amines.

19.6 Maleic acid is not a member of the saturated series but is considered here because of its relation to succinic acid, which it yields by hydrogenation. Maleic acid is manufactured in considerable quantities by the catalytic oxidation of benzene with air (Sec. 5-13), the actual product being mainly maleic anhydride:

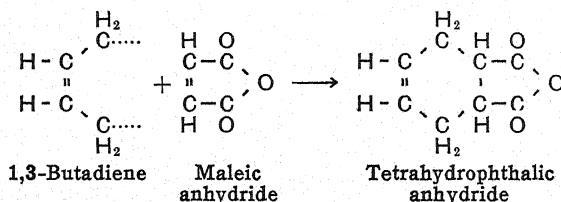


This acid and its anhydride are used extensively in producing alkyd resins (Sec. 24-14).

The ease with which maleic acid yields a cyclic anhydride suggests that it has the *cis* configuration (Sec. 15-24) with the COOH groups on the same side of the molecule. This is confirmed by other evidence. Fumaric acid, the *trans* isomer, sublimes at 287°C when heated in a sealed tube. It yields no anhydride, but when heated to 250 to 300°C in an open vessel it is slowly converted into maleic anhydride and decomposition products. That is, resistance to rotation about the double bond can be overcome by the absorption of energy. Fumaric acid has the lower solubility, the lower heat of combustion, and is the weaker acid as is generally true of the *trans* isomer of any *cis-trans* pair.

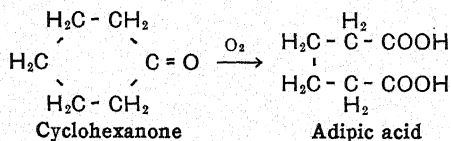


Diels-Alder Reaction.¹ Maleic anhydride takes part in an interesting and important reaction in which a *conjugated* diene reacts by 1,4-addition with the C=C bond of the anhydride, *e.g.*,



This reaction, which is effected by heating the two compounds together, has found numerous applications both in laboratory syntheses and in industry. Many different conjugated dienes may be used, and maleic anhydride can be replaced by other compounds in which a C=C bond is activated by a neighboring strongly electronegative group (*e.g.*, acrylonitrile). The Diels-Alder reaction serves also as a *test* for conjugated double bonds since only compounds containing that system will add to maleic anhydride.

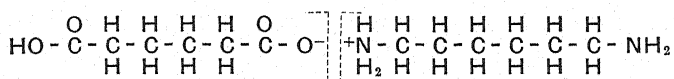
19-7 Adipic Acid; Nylon. Adipic acid, $\text{HOOC}(\text{CH}_2)_4\text{COOH}$, can be made by oxidizing cyclohexane, cyclohexanol, or cyclohexanone, *e.g.*,



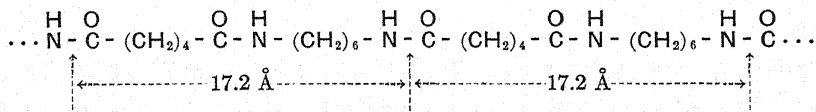
¹ Discovered in 1928 by Prof. Otto Diels of the University of Kiel and his associate Kurt Alder, who were awarded the Nobel prize in chemistry for 1950 in recognition of its many important applications.

The reaction just shown is entirely analogous to the oxidation of any other ketone; that is, the bond between the carbonyl carbon and one of its neighbors is split and both carbon atoms are oxidized to COOH groups. Adipic acid is now produced in very large quantities by the catalytic oxidation of cyclohexane from petroleum, for use in the manufacture of nylon.

Nylon is a polyamide made from adipic acid and hexamethylenediamine (1,6-diaminohexane). When these are mixed they unite like any other acid and amine to form a substituted ammonium salt. The simplest molecule has the structure



But the COOH group at one end of the molecule is capable of reacting in like manner with another molecule of amine, and the NH₂ group at the other end can react with adipic acid—and so on, repeatedly. This long-chain addition product is called *nylon salt*. When heated at 280°C, it reacts like ammonium acetate in splitting out water to form amide linkages. The resulting polyamide is *nylon*, a portion of the molecule of which is represented by the formula



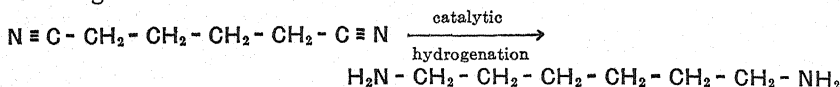
The molecular weight of the nylon used in making textile filaments is of the order of 12,000 to 20,000, corresponding to chains of some 50 to 90 of the fundamental unit C₁₂H₂₂N₂O₂. (This unit gives a "repeat" of 17.2 Å in X-ray diffraction diagrams.) Filaments are produced by extruding *melted*¹ nylon through small holes into air, which quickly chills them; they are then cold-drawn to about five times their original length. This stretching not only gives finer and more lustrous filaments but greatly increases their strength (to the high tenacity of about 5.7 grams per denier) by better alignment of the molecules. Nylon yarn for spinning and knitting consists of many fine filaments. Larger monofilaments are produced in a similar way for use as artificial bristles, etc.

Nylon is of interest as the first widely used, man-made fiber which is truly synthetic; rayon, it will be recalled, utilizes the long cellulose mole-

¹ Nylon differs physically from cotton, silk, and wool in that it can be melted (at 263°C). This is due to the absence of highly polar groups—OH, NH₂, COOH—which lead to strong hydrogen bonding crosswise between molecules of the others. The same fact probably explains why nylon is hard to wet. There is, however, some evidence of weak hydrogen bonds between CO and NH groups of adjacent molecules.

cules which occur in nature. Nylon was also the first filament to be produced by *melt* spinning, a technique now used also with Dacron, Saran, and some other synthetic fibers.

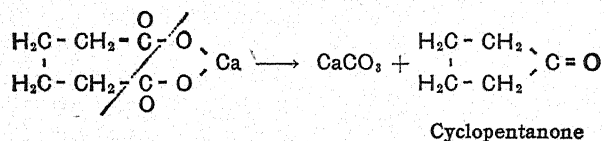
The diamine required for making nylon was manufactured originally from adipic acid by dehydrating its ammonium salt to the dinitrile and reducing:



The nitrile is now produced more cheaply by reaction between sodium cyanide and 1,4-dichlorobutane, obtained through furfural (Sec. 26-10) from corncobs and oat hulls.

The above description refers to the nylon ordinarily used. This is sometimes described as Nylon-66 because there are six carbon atoms in the acid and six in the amine. Many polyamides of analogous structures and more-or-less similar properties have been made by condensing other dibasic acids and diamines, *e.g.*, Nylon-610, from $\text{H}_2\text{N}(\text{CH}_2)_6\text{NH}_2$ and $\text{HOOC}(\text{CH}_2)_8\text{COOH}$, sebacic acid. Some of these are produced in small amounts for special uses.

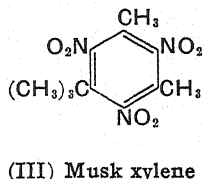
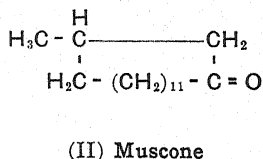
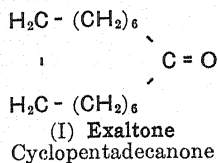
19-8 Cyclic Ketones. Adipic acid does not yield either a cyclic anhydride or a cyclic imide, and this is true likewise of the other acids in which COOH groups are *separated by four or more carbon atoms*. When the calcium salt of adipic acid is strongly heated, calcium carbonate is split out¹ with the formation of cyclopentanone:



Many other cyclic ketones have been prepared (usually with very poor yields) by a similar method in which the *thorium* salts of long-chain dicarboxylic acids are heated under reduced pressure. These include Exaltone (I) and others containing up to 34 carbon atoms in the ring. These cyclic ketones can be reduced by the Clemmensen method to the corresponding large-ring cyclanes, which are best obtained in this way. Both the ketones and the hydrocarbons are quite stable, showing no evidence of strain, and thus indicating that all such large rings are of the crumpled or puckered type (Sec. 4-6). Exaltone has the odor of natural musk, a highly prized—and highly priced—secretion of the musk deer,

¹ Compare with the old method for making acetone by heating calcium acetate (Sec. 10-3, paragraph 1).

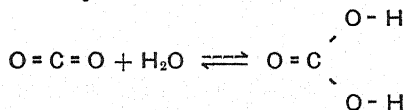
the odorous component of which is the ketone muscone (II). Several musk substitutes (so-called "synthetic musks")



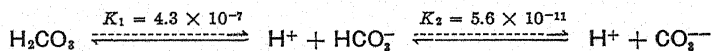
are now manufactured for use in the perfume industry. Musk xylene (III) is a typical example. These compounds differ widely from real musk in their molecular structures but have powerful musklike odors. Aside from contributing odor, musk and its synthetic substitutes serve as *fixatives* in perfumes; that is, they prevent the too rapid evaporation of certain components and blend them into a more lasting fragrance.

ORGANIC DERIVATIVES OF CARBONIC ACID

19-9 Carbonic acid, H_2CO_3 , is the simplest dibasic acid among the compounds of carbon. It is known only in solution, where equilibrium lies far to the left in the system:



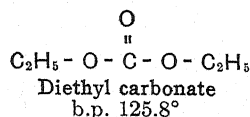
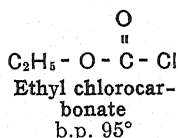
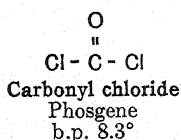
In other words, H_2CO_3 has the instability usually observed in compounds in which two hydroxyl groups are attached to the *same* carbon atom, and like the others, it readily loses a molecule of water. In solution, H_2CO_3 functions as an extremely weak dibasic acid, as indicated by the equilibrium constants for the system:



This weakness explains why H_2CO_3 is liberated when a carbonate is treated with any stronger acid, even acetic; instability accounts for the fact that CO_2 and H_2O are the actual products obtained.

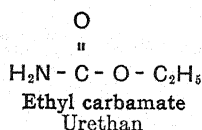
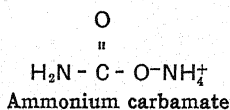
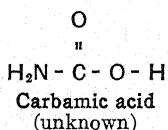
In spite of its instability and its low degree of ionization, carbonic acid yields many important derivatives, both inorganic and organic. The former are its salts, the bicarbonates and normal carbonates, such as NaHCO_3 , CaCO_3 , etc. Calcium carbonate and magnesium carbonate are among the most abundant substances in the crust of the earth; sodium carbonate (soda ash, Na_2CO_3) is one of the most widely used industrial chemicals.

19-10 Organic Derivatives. Many stable organic compounds are, structurally, derivatives of this highly unstable carbonic acid. Among these are found substantially all the types of simple and mixed compounds to be expected on the assumption that either or both OH groups can react like the one in a carboxylic acid. In general, these compounds can be prepared only by indirect methods.

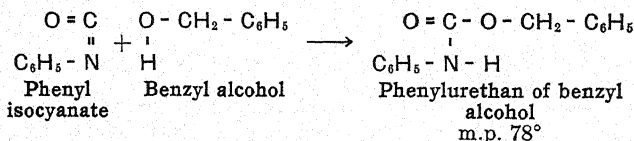


Carbonyl chloride, usually called phosgene, is made by addition between chlorine and carbon monoxide in sunlight or with a catalyst. It is a highly reactive acid halide which is valuable in organic synthesis. It was introduced as an effective war gas (lung irritant) in 1915.

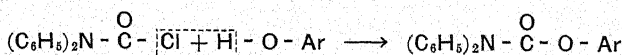
Ethyl chlorocarbonate, a mixed ester and acid halide, is best prepared by adding ethyl alcohol to chilled carbonyl chloride. The normal ester, *diethyl carbonate*, is prepared by heating ethyl iodide with silver carbonate. *Carbamic acid*, the monoamide of carbonic acid, has never been obtained, but its salts and esters are well known:



Urethans are the *O*-esters of carbamic acid and of *N*-substituted carbamic acids. They are frequently prepared as derivatives for the identification of higher alcohols¹ and phenols by reaction with either phenyl or α -naphthyl isocyanate, *e.g.*,

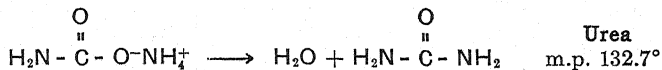


Diphenylurethans are made for the same purpose by reaction of an alcohol or a phenol with diphenylcarbamyl chloride:

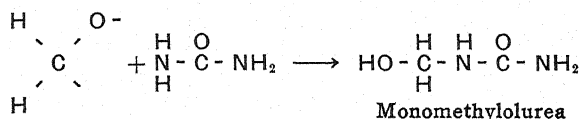


¹ They are not well suited for use with the lower alcohols, which are apt to contain water; isocyanates react with water to give insoluble disubstituted ureas.

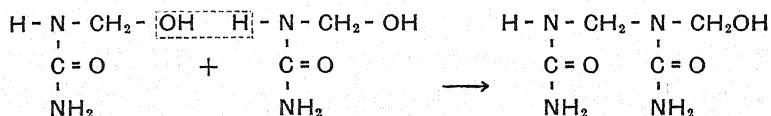
19.11 Urea, the most important organic derivative of carbonic acid, is the diamide. It is the principal nitrogenous compound in the urine of man and the other higher animals and was first isolated from that source. Urea is readily prepared in the laboratory by reaction between carbonyl chloride and ammonia but is manufactured by a high-pressure reaction between ammonia and carbon dioxide, in which ammonium carbamate is formed and dehydrated:



Urea is used as a fertilizer, as a stabilizer of smokeless powder and other nitrocellulose products, and for the manufacture of translucent plastics. Production of plastics depends upon a condensation between urea and formaldehyde which, in its initial stages, is represented by addition reactions of the type

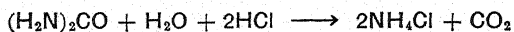


This is followed by condensation polymerization through the reaction



Repetition of these reactions leads to thermoplastic linear polymers. If excess of formaldehyde is used in the initial reaction, so that dimethylolurea ($\text{HOCH}_2.\text{NH}.\text{CO}.\text{NH}.\text{CH}_2\text{OH}$) is formed, thermosetting, crosslinked resins (Sec. 23.8) can be obtained.

Urea forms colorless crystals which are freely soluble in water and alcohol and insoluble in ether. It is a very weak base but yields well-defined salts with one molecule of strong acids. The nitrate is only sparingly soluble in water and can be obtained by concentrating urine by evaporation and adding cold nitric acid. Urea is hydrolyzed like other amides by superheated steam or by boiling with dilute alkali or acid:



Hydrolysis occurs also during the putrefaction of urine and in the soil when urea is used as a fertilizer; under these conditions the reaction is catalyzed by microorganisms or by enzymes which they secrete. The hydrolysis of urea to ammonia by the enzyme *urease* is a routine procedure in the analysis of blood and urine in medical laboratories.

Urea reacts with nitrous acid like other amides:

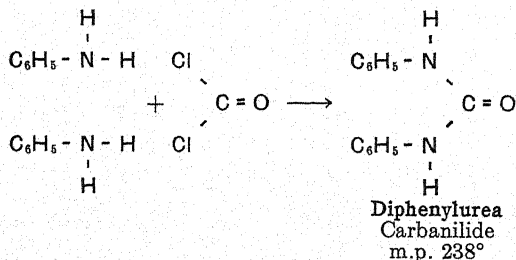


A similar reaction explains its use as a stabilizer in nitrocellulose products, where it functions by destroying the oxides of nitrogen which are slowly liberated during storage.

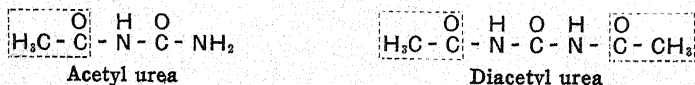
19-12 Wöhler's Synthesis. Urea was first prepared synthetically by Friedrich Wöhler (1828) when he heated together solutions of ammonium sulfate and potassium cyanate in the expectation of obtaining its isomer ammonium cyanate. He recognized that the actual product was identical with the *urea* which had been isolated from animal urine by Rouelle in 1773.

Accustomed as we now are to making all sorts of organic compounds in the laboratory, it is hard to understand why Wöhler's synthesis of urea is properly regarded as one of the great landmarks in the history of chemistry. But in 1828, the only organic compounds known were such as had been produced by *living* things—plants or animals. This fact had led to the belief that such compounds could be made *only* through the agency of a mysterious "vital force," supposed to reside in living cells. Wöhler's synthesis of urea was the first clean-cut demonstration that a typical animal product could be prepared in the laboratory from purely inorganic raw materials. It was shortly followed by laboratory preparations of various other compounds previously known only as plant or animal products. Thus, the theory of vital force was gradually abandoned and organic chemistry was freed from its paralyzing effects. The only trace of it that now remains is the term *organic* chemistry, which arose when the only source of such compounds was living or *organized* matter.

19-13 Derivatives of urea in which one or more hydrogen atoms are replaced by hydrocarbon radicals are known as *substituted ureas*. For example, diphenylurea is made by reaction between carbonyl chloride and aniline, just as urea is formed from carbonyl chloride and ammonia:

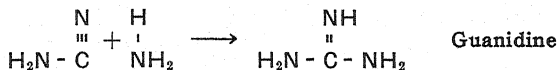


Ureides are acyl derivatives of urea, such as



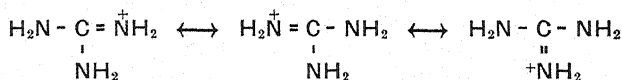
The most important of these are cyclic compounds, including uric acid (Sec. 26-12) and the sleep-inducing drugs derived from barbituric acid (Sec. 19-14).

Guanidine may be regarded as derived from urea by replacing the oxygen atom by the imino group, =NH. It can be prepared by reaction between ammonia and cyanamide:¹



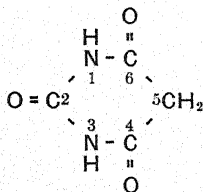
Substituted guanidines are obtained by similar reactions between cyanamide and amines. The guanidine group occurs in one of the biologically important amino acids, arginine (Table 21.1), and in the drug sulfaguanidine.

Guanidine is noteworthy for its exceptional strength as a base—which is comparable to that of oxalic acid as an acid. This is due to the high stabilization of the guanidinium ion by resonance between the three equivalent forms:

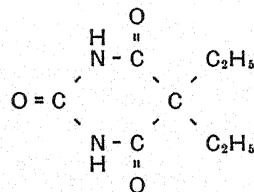


X-ray spectroscopy of guanidinium salts give the same value, 1.18 Å, for each of the carbon-nitrogen bonds. Normal values for C—N and C=N bonds are 1.48 and 1.28 Å, respectively. Guanidine is ordinarily used in the form of one of its salts, such as the hydrochloride; the free base, a crystalline solid melting around 50°C, is extremely hygroscopic and tends to polymerize.

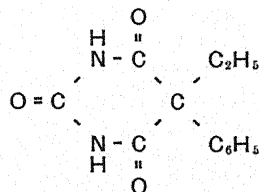
19.14 Barbituric Acid Derivatives. Malonic ester condenses with urea in the presence of sodium ethoxide to form the *cyclic* ureide commonly called barbituric acid and represented by formula (I). Many derivatives of barbituric acid, such as (II) and (III), have been prepared in like manner by using substituted malonic esters of the type $\text{RR}'\text{C}(\text{COOC}_2\text{H}_5)_2$. Most of these esters are obtained through the malonic ester synthesis (Sec. 20.19).



(I) Barbituric acid
Malonyl urea



(II) Barbital; Veronal
5,5-Diethylbarbituric acid

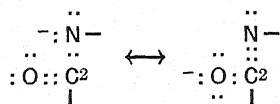


(III) Phenobarbital;
Luminal
5-Ethyl-5-phenylbarbituric acid

¹ Calcium cyanamide, CaCN_2 , is manufactured extensively by heating calcium carbide with nitrogen in the electric furnace. It is an important nitrogenous fertilizer—water in the soil converts it into urea—and a source of sodium cyanide, urea, acrylonitrile, and other intermediates for the organic-chemicals industry.

Derivatives of barbituric acid in which the hydrogen atoms of the CH_2 group have been replaced by hydrocarbon radicals have hypnotic and sedative properties, and a number of them are used as sleep-inducing drugs. The first to be used, the diethyl compound, was introduced in 1903 under the name Veronal as a result of the work of Emil Fischer. This is effective but so strongly habit-forming that it is no longer sold except on prescription. Phenobarbital is now used most extensively, with smaller amounts of ten or more others.

Barbituric acid contains neither a carboxyl nor a phenolic hydroxyl group but is a stronger acid ($K_a = 1 \times 10^{-4}$) than acetic and readily forms a monosodium salt. Acidity is ascribed to resonance in the anion which is formed when a proton is lost, *e.g.*,



The derivatives of barbituric acid behave similarly and are often used in the form of their soluble salts (*e.g.*, phenobarbital sodium).

Questions

1. (a) Describe the dicarboxylic acids in terms of their structural relations to the corresponding hydrocarbons. (b) Explain why aliphatic acids, whether containing one or two carboxyl groups, are seldom prepared in the way suggested by this relationship.

2. Review the effects on physical properties which result when one methyl group of ethane is converted into carboxyl (Table 11.2). From the physical properties of oxalic acid and its homologues, would you say that these effects are, roughly, additive when a second carboxyl group is introduced? Give specific reasons.

3. Using electronic formulas, explain in detail the origin of the exceptional strength of oxalic acid.

4. What is the relationship between the neutralization equivalent and the molecular weight of a dibasic acid?

5. (a) Distinguish between the terms "anhydrous acid" and "acid anhydride." (b) Anhydrous oxalic acid is more soluble in ether than is the ordinary crystalline compound. On what grounds could this fact be predicted?

6. (a) In just what way is the structure of oxalic acid unusual? (b) Describe three chemical properties in which oxalic acid differs from most other carboxylic acids. (c) Oxalic acid is formed by the hydrolysis of cyanogen, $(\text{CN})_2$. Write the equation and describe cyanogen as a derivative of oxalic acid.

7. (a) Write full equations for the synthesis of malonic acid from chloroacetic acid. (b) Show what happens when malonic acid is strongly heated. (c) Write the structural formulas of two other acids which, when heated, will act like malonic acid.

8. (a) In the preparation of succinic acid from bromoacetic acid by the Wurtz-Fittig principle, what advantage is there in the use of metallic silver instead of zinc or sodium? (b) Write full equations for the preparation of succinic acid from ethylene-dibromide. (c) Given bromosuccinic acid, suggest a practical method for preparing

an isomer of glutaric acid. (d) From any desired halogen-substituted *n*-butyric acid, show how to prepare glutaric acid.

9. (a) Write the structural equations for the formation of succinic anhydride and glutaric anhydride. (b) What structure is common to all acids that form cyclic anhydrides on heating? (c) Explain in terms of space relations. (d) Write the formulas of two acids, other than succinic and glutaric, which form cyclic anhydrides and imides.

10. Assuming that they are analogous to those of acetic anhydride, write structural equations for the reactions to be expected when succinic anhydride is treated with: (a) boiling water; (b) ammonia; (c) ethyl alcohol; (d) ethylene glycol.

11. Write structural equations for the Diels-Alder condensation between maleic anhydride and: (a) isoprene; (b) cyclopentadiene.

12. Write equations for all steps in the manufacture of hexamethylenediamine (1,6-diaminohexane) from 1,4-dichlorobutane.

13. Show that the conversion of nylon salt into nylon is analogous to the formation of acetamide from ammonium acetate.

14. (a) It has been noted that azelaic acid (C_9) is one of the products of the oxidation of oleic acid (Sec. 15-21). Write the structural equation for the reaction to be expected when the calcium or thorium salt of azelaic acid is heated. (b) Discuss the use of long-chain dicarboxylic acids as sources of alicyclic ketones and hydrocarbons containing large rings. (c) Suggest a reason why the calcium and thorium salts of these acids give better yields of cyclic ketones than do sodium and potassium salts.

15. Show that monocarboxylic acids or their salts undergo the same types of reactions (decarboxylation, anhydride formation, and ketone formation) exhibited by malonic, succinic, and adipic acids.

16. In exactly what ways do formic acid, carbonic acid, and oxalic acid differ in their structures from all other compounds containing a carboxyl group?

17. Express in words the structural relations of the following to carbonic acid: sodium bicarbonate, sodium carbonate, carbonyl chloride, urea, diethyl carbonate, ethyl chlorocarbonate, carbamic acid, urethans.

18. (a) Show that the formation of urea by reaction between carbonyl chloride and ammonia is entirely analogous to the most general method for making simple amides. (b) Show that the reactions of urea with nitrous acid and with hydrolyzing agents are comparable to those of other amides. (c) Write the full series of reactions that take place in the soil when urea, from urine or from a commercial fertilizer, is hydrolyzed to an ammonium salt (plant food).

19. Distinguish, with examples, between the terms "substituted urea" and "ureide."

20. (a) Account for the strength of guanidine as a base. (b) Account for the acidic properties which make possible the existence of the drug phenobarbital sodium.

CHAPTER 20

SUBSTITUTED ACIDS; TAUTOMERISM

Substituted acids contain a carboxyl and some other functional group. They are named as substitution products of simple carboxylic acids as illustrated below. Positions of substituents are shown either by the official numbering system, in which C¹ is that of the COOH group, or by Greek letters, the *alpha* carbon being the one *next* to the COOH group (cf. footnote page 185).

20.1 Types and General Properties. The more important types of substituted aliphatic acids are described and illustrated as follows:

Halogen-substituted acids:	$\begin{array}{c} \text{H} \quad \text{O} \\ \quad \\ \text{Cl} - \text{C} - \text{C} - \text{OH} \\ \\ \text{H} \end{array}$	Chloroacetic acid
Hydroxy acids:	$\begin{array}{c} \text{H} \quad \text{H} \quad \text{O} \\ \quad \quad \\ \text{H} - \text{C} - \text{C} - \text{C} - \text{OH} \\ \quad \\ \text{H} \quad \text{OH} \end{array}$	α -Hydroxypropionic acid Lactic acid
Aldehyde and keto acids:	$\begin{array}{c} \text{H} \quad \text{O} \quad \text{H} \quad \text{O} \\ \quad \quad \quad \\ \text{H} - \text{C} - \text{C} - \text{C} - \text{C} - \text{OH} \\ \quad \quad \\ \text{H} \quad \quad \text{H} \end{array}$	β -Ketobutyric acid Acetoacetic acid
Amino acids:	$\begin{array}{c} \text{H} \quad \text{O} \\ \quad \\ \text{H}_2\text{N} - \text{C} - \text{C} - \text{OH} \\ \\ \text{H} \end{array}$	Aminoacetic acid Glycine
Cyano acids:	$\begin{array}{c} \text{H} \quad \text{O} \\ \quad \\ \text{N} \equiv \text{C} - \text{C} - \text{C} - \text{OH} \\ \\ \text{H} \end{array}$	Cyanoacetic acid

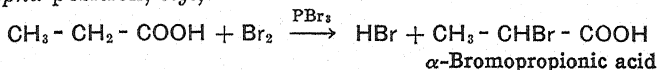
Many of the chemical properties of these acids can be predicted from the behavior of their functional groups in simple molecules. The carboxyl group usually reacts to yield the salts, esters, acid halides and other types of derivatives to be expected; this is illustrated by the six classes of derivatives still containing the chlorine atom which can be formed from chloroacetic acid (Sec. 20.3). The other functional groups (Cl, OH, NH₂, etc.) likewise exhibit their customary reactions. The more important exceptions to this general rule will be described.

Amino acids are not considered in this chapter but are deferred for study in connection with the proteins (Chap. 21), to which they are intimately related.

HALOGEN-SUBSTITUTED ACIDS

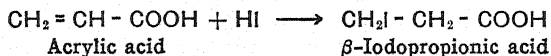
20.2 Preparation. Some of the more general methods for preparing halogen-substituted acids are the following:

1. *From saturated acids*, by direct substitution of chlorine or bromine in the *alpha* position, *e.g.*,



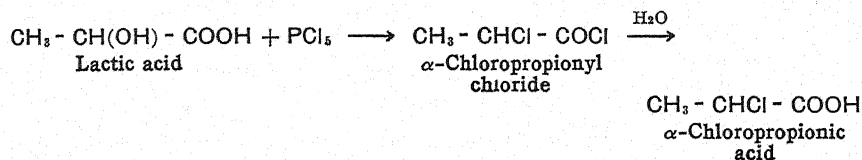
Reaction proceeds smoothly in the presence of a little PBr_3 and, by controlling the amount of bromine used, either the mono- or dibromo acid can be obtained in good yield. This ready substitution by chlorine or bromine is a further illustration of the special reactivity of hydrogen atoms on a carbon *alpha* to a $\text{C}=\text{O}$ group. Halogen substitution in *beta* and more remote positions occurs no more readily than in the parent alkanes. Acetic acid, which has three α hydrogen atoms, is easily chlorinated in the presence of a little iodine or red phosphorus to give chloroacetic, dichloroacetic, or trichloroacetic acid. The last is best obtained, however, by oxidizing chloral with nitric acid.

2. *From unsaturated acids*, by addition of chlorine, bromine, or a hydrogen halide at the $\text{C}=\text{C}$ bond. In the addition of hydrogen halides to *alpha-beta* unsaturated acids the halogen atom adds in the β position, *e.g.*,



If the $\text{C}=\text{C}$ bond is farther from the carboxyl, the direction of addition is more a matter of chance.

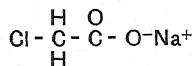
3. *From hydroxy acids*, by replacement of the hydroxyl group. This is the net result of treating a hydroxy acid with a phosphorus halide, *e.g.*,



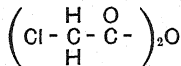
Phosphorus halides replace hydroxyl by halogen both in alcohols and in acids and, therefore, replace both OH groups in hydroxy acids. But when a chloroacid chloride such as $\text{CH}_3\text{CHClCOCl}$ is treated with water, the much more reactive *acyl* halogen atom is quickly hydrolyzed off and the chlorine-substituted acid obtained.

20-3 Chloroacetic acid is the best known and most important halogen-substituted acid. It is manufactured by passing chlorine into glacial acetic acid at around 100°C in the presence of a little red phosphorus until the density shows that monochlorination is substantially complete. The acid is a crystalline solid which is freely soluble in water. The chemical properties of chloroacetic acid, as outlined below, are typical of other α -halogen-substituted acids.

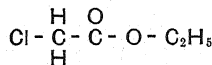
The *carboxyl group* enters into all its usual reactions, yielding the following types of *acid derivatives* in which the halogen atom is retained. These compounds are analogous to the corresponding derivatives of acetic acid and are made by similar methods:



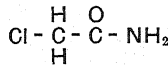
Sodium chloroacetate



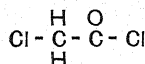
Chloroacetic anhydride



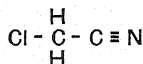
Ethyl chloroacetate



Chloroacetamide

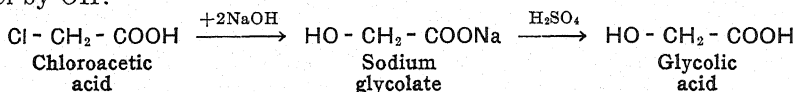


Chloroacetyl chloride

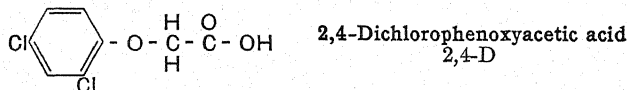


Chloroacetonitrile

The chlorine atom of chloroacetic acid enters into the usual replacement reactions of the alkyl halides. Boiling, dilute NaOH solution¹ replaces Cl by OH:



Strong ammonia replaces Cl by NH₂ to give glycine, H₂N.CH₂.COOH, and a similar reaction with aniline yields phenylglycine, C₆H₅.NH.CH₂.COOH. The replacement of Cl by CN was illustrated in the preparation of malonic ester (Sec. 19.4). Reaction with phenoxides yields aryloxyacetic acids, *e.g.*,



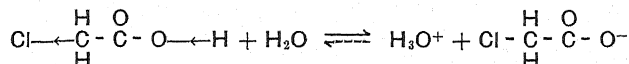
Large amounts of this acid and several of its salts and esters are manufactured for use as the herbicide 2,4-D. These act as hormones and kill broad-leaved plants by overstimulation.

20.4. Mutual Influences. The halogen atom in an *alpha*-substituted

¹ It is important to bear in mind that, as with any other acid, *neutralization* is the initial effect of treating a halogen-substituted acid with an alkali, ammonia, or sodium carbonate. Being ionic, this reaction is completed within the time required for mixing. The reaction between an excess of alkali or ammonia and the halogen atom of the organic anion is a much slower subsequent process which usually requires heat. When it has been accomplished, a mineral acid is added and the carboxylic acid is liberated from its salt. Thus the initial effect of alkali on the carboxyl group is reversed, and the *net result* of the three reactions amounts to the simple replacement of halogen by hydroxyl. Similar series of reactions are involved in the replacement of halogen by reactions with ammonia and the amines.

acid is replaceable much more easily than in a corresponding alkyl halide. This can be attributed to electron attraction by the adjacent carboxyl group, which gives the α carbon atom a relatively high $+\delta$ charge. Thus it is more readily attacked by hydroxyl ion, ammonia, and other nucleophilic reagents. In the *beta* position this influence is much less marked and, in more remote positions, it disappears.

Conversely, electron attraction by an α halogen atom increases ionization of the COOH group; *e.g.*, the ionization of chloroacetic acid is about nine times that of acetic acid under the same conditions. Induction by the chlorine atom displaces all electrons in the molecule (toward the left as the formula is written below) including the pair that bonds the OH hydrogen atom. Hence the latter is more readily removed as hydronium ion:



The effect of induction by halogen atoms is further illustrated by Table 20-1; this shows that acid strength increases with the electronegativity

TABLE 20-1 IONIZATION OF HALOGEN-SUBSTITUTED ACIDS

Substituents	Acid	$K \times 10^{\dagger}$
<i>Nature</i>		
None.....	H.CH ₂ .COOH (acetic)	1.76
Iodine.....	I.CH ₂ .COOH (iodoacetic)	71
Bromine.....	Br.CH ₂ .COOH (bromoacetic)	135
Chlorine.....	Cl.CH ₂ .COOH (chloroacetic)	155
Fluorine.....	F.CH ₂ .COOH (fluoroacetic)	210
<i>Position</i>		
None.....	CH ₃ .CH ₂ .CH ₂ .COOH	1.5
<i>Alpha</i>	CH ₃ .CH ₂ .CH ₂ Cl.COOH	139
<i>Beta</i>	CH ₃ .CHCl.CH ₂ .COOH	9
<i>Gamma</i>	CH ₂ Cl.CH ₂ .CH ₂ .COOH	3
<i>Number</i>		
None.....	CH ₃ .COOH	2.45 \dagger
One.....	CH ₂ Cl.COOH	22.5 \dagger
Two.....	CHCl ₂ .COOH	70 \dagger
Three.....	CCl ₃ .COOH	89.5 \dagger
Three.....	CF ₃ .COOH	100 \dagger

\dagger The comparative strength of two acids, or their relative degree of ionization at the same concentration, is equal to the *square root* of the ratio of their ionization constants. Chloroacetic acid is 9.4 times as highly ionized as acetic acid since $\sqrt{155/1.76} = 9.4$.

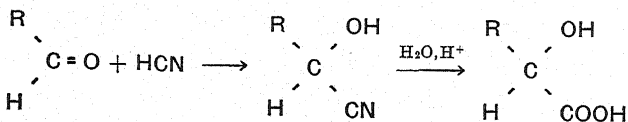
\dagger In per cent ionized. These data are for 0.03 *M* solutions at 25°C. Comparisons are made in this way because di- and trichloroacetic acids are so strong that true ionization constants cannot be calculated for water solutions. Trifluoroacetic acid appears to be completely ionized in any water solution, just as is HCl.

of the halogen and with the number of halogen atoms, and decreases sharply as the substituent is moved away from the *alpha* position.

HYDROXY ACIDS

20-5 Sources and Synthesis. Some hydroxy acids (tartaric, citric) are relatively abundant in plants, and some (lactic, citric) are readily obtained by the fermentation of natural products. The more important general methods of preparation are:

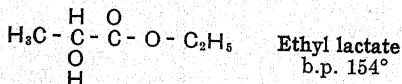
1. From *polyhydric alcohols* by regulated oxidation.
2. From *aldehyde acids* and *keto acids* by reduction.
3. From *halogen-substituted acids* by hydrolysis.
4. From *amino acids* by the action of nitrous acid.
5. From *unsaturated acids* by addition of water at the C=C bond.
6. From *aldehydes* and *ketones* by addition of hydrocyanic acid and hydrolysis of the resulting cyanohydrin:



This is one of the best ways to make *alpha* hydroxy acids but is necessarily limited to this class because its products have the OH and COOH groups attached to the *same* carbon atom.

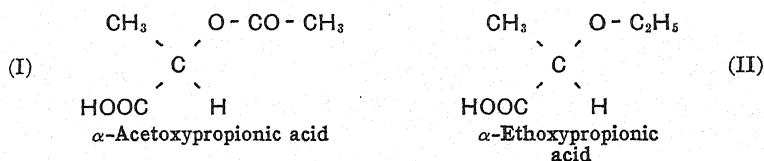
20-6 Lactic acid, $\text{CH}_3\text{CHOH}\cdot\text{COOH}$, or α -hydroxypropionic acid, was isolated from sour milk by Scheele in 1780. It is formed there by the action of bacilli, such as *Bacillus acidi lactici* on milk sugar (lactose). Lactic acid is now manufactured from glucose, cane sugar, or maltose by *Bacillus delbrucki*. The "fermentation" lactic acid ordinarily produced¹ by these methods is the DL-racemate. This is a colorless viscous liquid (m.p. 16.8°C; b.p. 122°C^{15mm}; *d*, 1.249) which is freely miscible with water, ethyl alcohol, and ether. It is marketed as a concentrated aqueous solution for use in tanning and dyeing, in foodstuffs and pharmaceuticals, and in the manufacture of its salts and esters.

Most of the reactions of lactic acid are those to be expected of a compound related as it is to propionic acid and to isopropyl alcohol. The *carboxyl* group can be neutralized to yield salts (lactates) and is also esterified under the usual conditions to form esters with various alcohols, *e.g.*,



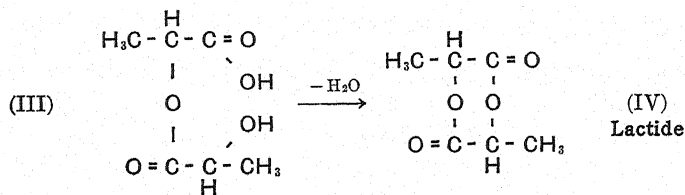
¹ Some bacteria, acting on certain sugars, give one of the optically active lactic acids.

When allowed to stand with concentrated ammonia, ethyl lactate is converted into lactamide, $\text{CH}_3\text{CHOH.CO.NH}_2$ (m.p. 74°C). The secondary *alcohol* group in lactic acid can be reduced, yielding propionic acid, and *esterified* by the usual reaction with acyl halides to give compounds such as (I). Working through a carboxylic ester, the principle of the Williamson synthesis may be used to *etherify* the OH group and form derivatives such as (II).



The reaction with phosphorus halides, which replace both hydroxyl groups, was described above. Lactic acid does not form an anhydride but reacts on heating as follows.

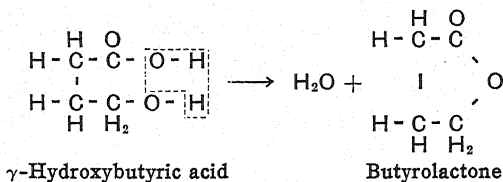
20.7 Dehydration of Hydroxy Acids. When lactic acid is heated, the initial reaction is a typical esterification—the elimination of water between the COOH group of one molecule and the alcoholic OH group of another, to form (III):



The ester (III) can react with other molecules of lactic acid, either through its OH or its COOH group, to form a linear polyester. Prevailing, however, the acid and alcohol groups in (III) react with each other to form the cyclic *diester* (IV) called *lactide*. The formation of lactides is characteristic of, and limited to, *alpha* hydroxy acids.

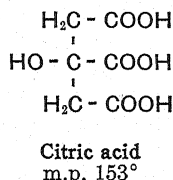
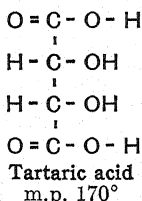
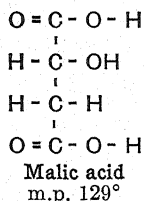
β-Hydroxy Acids. When *β*-hydroxypropionic acid is heated it loses water, forming acrylic acid, $\text{H}_2\text{C}=\text{CH.COOH}$. This ready dehydration is common to those *β*-hydroxy acids which have at least one hydrogen atom in the activated *α* position. The reaction therefore serves as a fairly general method for preparing *α,β*-unsaturated acids.

γ-Hydroxy and *δ-hydroxy acids* split out a molecule of water between the carboxyl and hydroxyl groups of the *same* molecule, to form cyclic esters known as *lactones*, e.g.,



The formation of *gamma* lactones, containing five-membered rings, occurs so readily that these are often the products obtained from reactions intended to yield γ -hydroxy acids. The tendency to form the six-membered rings of δ -lactones is much less. The ring structure of lactones is relatively stable, and the ester linkage is only slowly and incompletely hydrolyzed by boiling with water or dilute acids; hot alkalies open the ring, forming salts of the corresponding hydroxy acids.

20.8 Polybasic Hydroxy Acids. Three acids of this type, all occurring in nature, are of considerable importance. These are



Malic acid gets this name from its occurrence in apples (L., *malum*). It can be prepared from bromosuccinic acid and similar compounds by the usual general methods but is manufactured by heating maleic acid with steam under pressure. Malic acid is used like citric acid in food products.

Tartaric acid occurs in the juice of grapes as the dextrorotatory isomer (Sec. 17-12). During the alcoholic fermentation of wine making the increasing concentration of ethyl alcohol throws out of solution sparingly soluble potassium hydrogen tartrate. This deposit, containing various impurities and known as *crude argols*, is the industrial source of tartaric acid and its salts. These include: purified potassium hydrogen tartrate (*cream of tartar*), the sodium potassium salt (*Rochelle salt*), and the potassium antimonyl (SbO) salt known as *tartar emetic*.

Citric acid is the best known acid containing three carboxyl groups. It occurs in the juices of citrus fruits and formerly was obtained mainly from lemons. It is now manufactured in large quantities by the fermentation of sugar solutions by microorganisms (a special strain of the mold *Aspergillus niger*). Citric acid is harmless in the animal body, where it is readily oxidized. For this reason it is used extensively in food products (soft drinks, confectionery) and in pharmacy.

20-9 Fehling's Solution; Benedict's Solution. The hydroxyl groups in tartrate and citrate ions react with metallic hydroxides to form complex anions. This reaction is utilized in preparing useful test solutions, as follows.

Fehling's solution is prepared as needed by mixing a solution of cupric sulfate with a solution of sodium potassium tartrate and sodium hydroxide. (The proper concentrations are given in laboratory manuals.) As these are poured together there is usually some precipitation of pale blue hydrated cupric hydroxide. This dissolves on stirring, with formation of a soluble cupritartrate ion which colors the solution an intense purplish blue. The copper atom in this complex appears to be coordinated with two tartrate ions through the oxygen atoms of their four OH groups, giving a structure similar to (II) of Section 20-15. The cupritartrate ion is in equilibrium with a very low concentration of cupric ion (of the order of 1×10^{-13}) and serves as a reservoir to replenish the latter as it is removed by a reducing agent. Fehling's solution is used at boiling temperature in testing for reducing sugars, aldehydes, and other readily oxidizable compounds. Evidence of reaction is the deposition of cuprous oxide, Cu_2O , which appears as a red, yellow, or green precipitate depending on the rapidity with which it is formed and the consequent size of the particles. In quantitative determinations the precipitated cuprous oxide is collected by filtration and weighed as such or converted into metallic copper.

Benedict's solution is made from sodium citrate, sodium carbonate, and cupric sulfate solutions. It contains a cupricitrate ion which gives the solution a deep bluish-green color. Its uses are similar to those of Fehling's solution, to which it is generally preferred in medical laboratories.

KETO ACIDS; TAUTOMERISM

20-10 Pyruvic acid, $\text{CH}_3\text{CO.COOH}$, the simplest α -keto acid, is of great interest in biochemistry because it plays an important role in alcoholic fermentation and in the metabolism of carbohydrates and, probably, of proteins. The β -keto acids are all quite unstable in the free state, but their esters combine reasonable stability with high chemical activity. The ethyl ester of β -keto butyric acid, $\text{H}_3\text{C.CO.CH}_2\text{COOH}$, is selected for detailed study here, partly because of its uses in organic synthesis but mainly because it illustrates the phenomenon called tautomerism.

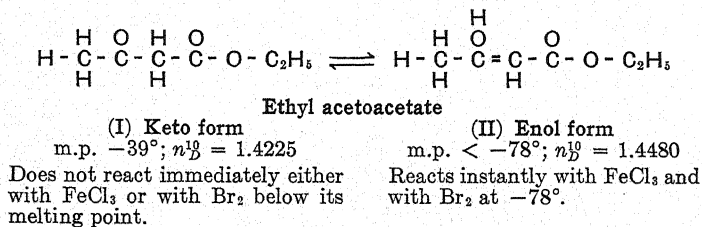
20-11 Tautomerism. The cornerstone of organic chemistry as a science is the conception that the atomic nuclei in each carbon compound have a definite fixed arrangement. On this basis we can understand the existence of different compounds, each with its own physical and chemical properties and each composed of the same numbers of the same kinds of atoms. Without it, isomerism cannot be explained.

Experience shows that isomers are not, in general, any more readily converted into one another than are other compounds. For example, ethyl ether is one of the last compounds we would choose for the preparation of its isomer, butanol. Many similar observations lead to the conclusion that, once having combined in a definite order to form a particular kind of organic molecule, atoms do not shift their positions.

While this conclusion summarizes the behavior of most carbon compounds, there are some which do change into isomers of different structures. If such a change is *reversible* and the isomers exist in *equilibrium*, it is described as *tautomeric*. Mutually convertible isomers are *tautomers*.

20-12 Ethyl acetoacetate, often called *acetoacetic ester*, afforded one of the earliest known examples of tautomerism. Every specimen was identical in its physical properties—*e.g.*, b.p. 180°C; *d*, 1.025; refractive index, 1.4232—and therefore appeared to represent a pure individual substance. But its chemical properties long presented a problem because they could not be explained in terms of any one structural formula. The compound is clearly an ester for it can be reduced to the ethyl ester of β -hydroxybutyric acid. It adds hydrocyanic acid and sodium bisulfite and gives various other reactions of ketones, as would be expected from the *carbonyl* group shown in (I). But ethyl acetoacetate gives other reactions which this formula neither suggests nor explains. It dissolves more freely in dilute alkali than in water and otherwise acts as a weak acid ($K_a = 2 \times 10^{-11}$); it yields an acetyl derivative with acetyl chloride in pyridine; and it gives a dark red color with ferric chloride solution. These properties suggest the presence of a *hydroxyl* group. Furthermore it decolorizes bromine rapidly—behavior characteristic of compounds containing the C=C double bond. Formula (II) suggests and accounts for these latter properties but cannot explain the ketone reactions.

The problem thus presented was finally solved by dissolving highly purified ethyl acetoacetate in petroleum ether and cooling to very low temperatures. By this means, it was separated into *two* compounds having the following structures and properties:

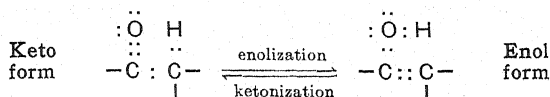


Either form can be kept unchanged for a long time below -78°C ; but at room temperature each passes into the same equilibrium mixture, containing about 8 per cent of the enol and 92 per cent of the keto compound. This illustrates the *reversible* interconversion of isomers, leading to an equilibrium, which differentiates tautomeric compounds from all ordinary mixtures.

Tautomerism is a phenomenon entirely distinct from resonance—although, as will be seen, resonance is usually involved. A specimen of benzene

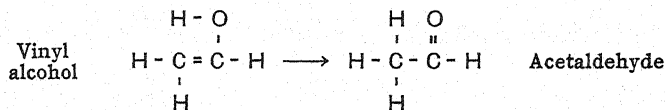
must be regarded as consisting of one kind of molecule only—a hybrid molecule with a structure intermediate between the two Kekulé forms. A specimen of ethyl acetoacetate on the other hand contains molecules of two *different* structures, each having its own distinctive properties. The extreme forms which contribute to the structure of a resonating molecule differ only in the positions of electrons. Tautomers differ in the position of an atomic nucleus—in most instances, a proton.

20-13 Keto-Enol Tautomerism. The over-all change in the tautomerism of ethyl acetoacetate is the transfer of a hydrogen atom from carbon to oxygen, and vice versa, accompanied by shifts of the double bond between the C=O and C=C types:



Any compound which contains either of these groupings is capable, theoretically, of similar *keto-enol*¹ tautomerism leading to an equilibrium mixture.

The equilibrium proportions of keto and enol forms are influenced greatly by the other atoms and groups attached to the fundamental tautomeric system shown above. The simplest conceivable enol, vinyl alcohol, has never been isolated, and all attempts to prepare it yield the keto tautomer (cf. Sec. 3-17):



The keto form predominates likewise in most other simple structures, *e.g.*, it has been estimated that acetone contains only about 2×10^{-4} per cent of enol. Certain compounds, however, approach the opposite extreme; acetyl acetone—which is usually represented by the diketo formula $\text{H}_3\text{C}.\text{CO}.\text{CH}_2.\text{CO}.\text{CH}_3$ —is 76 to 80 per cent enol in the liquid and 91 to 93 per cent in the gaseous state.

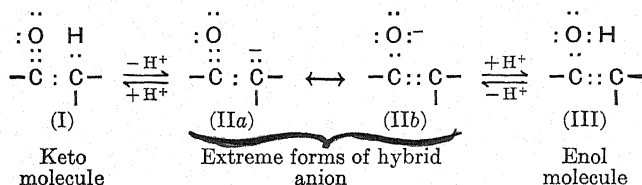
Tautomeric change is powerfully catalyzed by small amounts of bases and of acids. In the absence of catalysts it is relatively slow. This means, of course, that considerable time is required for pure specimens to come to equilibrium.

It has been reported that one especially pure (*i.e.*, catalyst-free) specimen of ethyl acetoacetate *enol* required 500 hours for half of it to pass into the keto form. This is an extreme example because it is seldom possible to attain and maintain the necessary purity.

¹ The term *enol* comes from the systematic nomenclature, where it is the termination for the names of unsaturated alcohols, *e.g.*, $\text{CH}_3.\text{CH}=\text{CH}(\text{OH})$, prop-*en-ol*.

20-14 Mechanism. Just *how* is a hydrogen atom transferred from carbon to oxygen, and vice versa, in keto-enol tautomerism? This is not, as was formerly supposed, a direct shift *within a molecule*. Such a shift does not account for the powerful catalytic effect of bases and acids. Nor can it explain how deuterium enters compounds tautomerizing in the presence of heavy water, D₂O.

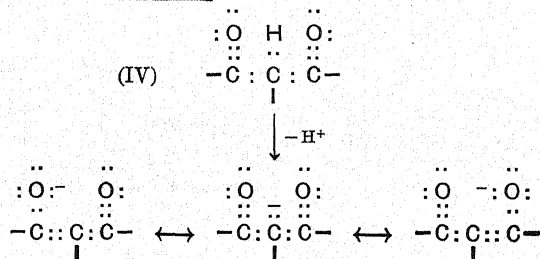
Base-catalyzed tautomerism begins with the removal of a proton by the catalyst. The same resonating anion (II) is formed whether the proton is taken from carbon in the keto molecule or from oxygen in the enol. This hybrid anion can react as either of its extreme forms, and a proton (or a deuteron, if present) may add either to carbon, producing a keto molecule, or to oxygen, giving the enol:



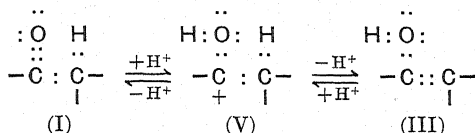
The formation of a hybrid anion is thus seen as the essential step in base-catalyzed tautomerism.

We are accustomed to the fact that OH hydrogen atoms are always more or less acidic and subject to removal by bases. An acidic hydrogen atom attached to carbon is more unusual but was encountered in the study of the aldol condensation (Sec. 10-9). There it was pointed out that a hydrogen atom *alpha* to a C=O group may be removed as a proton by alkalies. Now it becomes apparent that this is the particular grouping which occurs in every keto molecule capable of tautomeric change.

The acidity of a proton attached to carbon is increased in acetoacetic ester and other compounds which contain grouping (IV). Both carbonyl groups attract electrons from the central carbon, thus weakening its hold on hydrogen; and, when the proton is lost, the anion is stabilized by resonance between *three* forms:

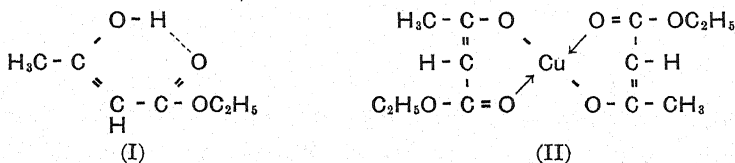


Acid-catalyzed tautomerism is explained by the following reversible system:



Either a keto molecule (I) or an enol molecule (III) can add a proton from an acid catalyst, forming the cation (V). The resulting plus charge attracts electrons both from the oxygen and the α carbon. Hence a proton is easily detached *from one or the other* as indicated. It should be noted that (V)—unlike (II)—is not a hybrid ion.

20-15 Chelation of Enols. Enolic ethyl acetoacetate is less soluble in water, more soluble in organic liquids, and has a considerably lower boiling point¹ than the keto tautomer. These are not the properties to be expected of the form containing an OH group; this should lend itself to hydrogen bonding with water, thus increasing solubility, and to molecular association and a higher boiling point. Such facts are evidence of *internal* hydrogen bonding as indicated in (I):



This cyclic structure is described as *chelated*.² It occurs in other compounds (cf. Sec. 23-10) so constituted that *six-membered* rings can result from hydrogen bonding or the formation of coordinate covalences. The green, crystalline compound which ethyl acetoacetate forms with cupric ions has the chelate structure shown in (II). This would explain why, unlike a *salt*, it is soluble in organic liquids. A characteristic test for enols is the deep red color which they give with ferric ions; in these colored complexes Fe^{+++} is probably coordinated by chelation with three enol molecules.

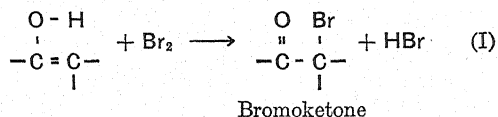
20-16 Estimation of Enols. Tautomeric equilibrium is displaced, as in any other dynamic system, by the addition of a reagent which can react with and thus remove either tautomer. Only the enol molecules (7.7 per cent) in an ordinary specimen of

¹ If ordinary ethyl acetoacetate (the equilibrium mixture) is distilled slowly, at 2 mm pressure, from a quartz flask, the distillate is much richer in enol and the higher boiling liquid remaining in the flask is *pure keto*. A quartz flask is necessary because even the best glass yields enough alkali to catalyze tautomeric change.

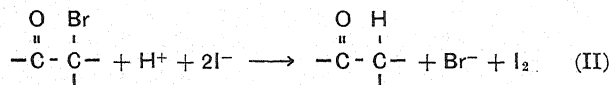
² Chelate (pronounced kēy-lāte) comes from a Greek word meaning claw, as of a crab.

ethyl acetoacetate can react with and decolorize bromine; but if bromine is added in some excess, its color fades as more enol molecules are formed and disappears after standing several minutes. Similarly the red color which the enol molecules give immediately with ferric chloride becomes more intense on standing. Conversely, reagents for ketones displace the equilibrium in the opposite direction.

These facts limit the chemical methods which may be used to measure the enol content of a specimen. Kurt Meyer's *bromine titration*, widely used, takes advantage of the fact that the rate at which an enol adds bromine is greater than the rate of enolization. Excess of a bromine solution in ethanol is poured into the cold specimen and reacts quickly with the enol, as follows:

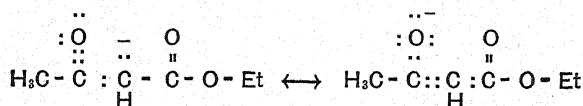


β -Naphthol is added immediately to take up the excess bromine. The amount of bromoketone formed in (I) is then determined by adding potassium iodide solution

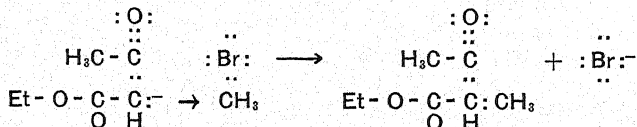


and titrating the liberated iodine with standard sodium thiosulfate solution. The percentage of enol in the sample is calculated from the result of titration.

20-17 Acetoacetic Ester Synthesis. This term serves to describe a number of reactions in which ethyl acetoacetate is used in making other compounds. We shall consider here only the preparation of acids and ketones. The initial step consists in adding 1 gram-atomic weight of sodium for each mole of the ester. The sodium dissolves slowly, with evolution of hydrogen, to give the ionized sodium salt of the hybrid anion:

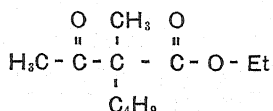


When one mole of an alkyl halide such as methyl bromide is now added, this anion unites with the alkyl radical through a nucleophilic attack, as follows:



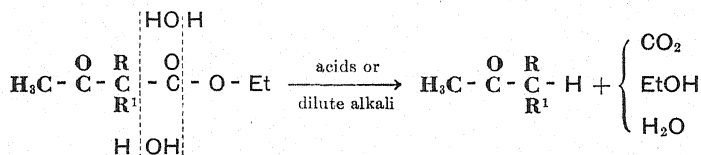
This *C*-methyl derivative of acetoacetic ester still contains an active hydrogen atom and can enolize. It will dissolve 1 gram-atomic weight of sodium per mole, and when this reaction is ended and a second mole of

alkyl halide added, a *C*-dialkyl derivative is formed. The use of butyl bromide in the last step gives



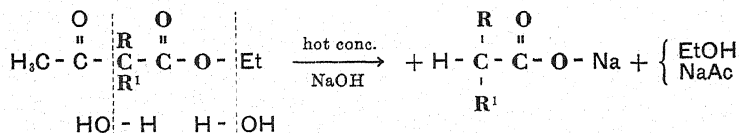
This sequence of reactions can be used to make a wide variety of substituted acetoacetic esters in which either one or both of the original methylene (CH_2) hydrogen atoms have been replaced by hydrocarbon radicals, alike¹ or different. These compounds can be converted into ketones or into acids, as follows.

Formation of Ketones. When ethyl acetoacetate or one of its monoalkyl or dialkyl derivatives is heated with an acid or a *dilute* solution of alkali, the molecule splits prevalingly in the sense of the equation



The product is always a *methyl* ketone, but the structure of the other hydrocarbon radical is determined by the alkyl groups that have been introduced. Many ketones not otherwise obtainable have been synthesized in this way.

Formation of Acids. Hot *concentrated* alkalies decompose acetoacetic ester and its derivatives in the entirely different way illustrated by the following type equation:



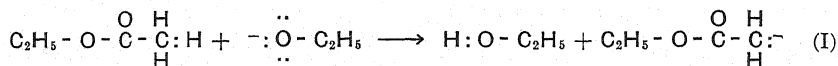
The products always include ethyl alcohol, sodium acetate, and the sodium salt of another acid. The structure of this second acid is determined by the number and nature of the alkyl radicals introduced into the ester. If, for example, two methyl groups are introduced, the sodium salt of isobutyric acid is obtained.

Because it is a method for the synthesis of acids, this second mode of reaction is often called the *acid* decomposition, although it is effected with the aid of concentrated alkali. The two types of reaction are more

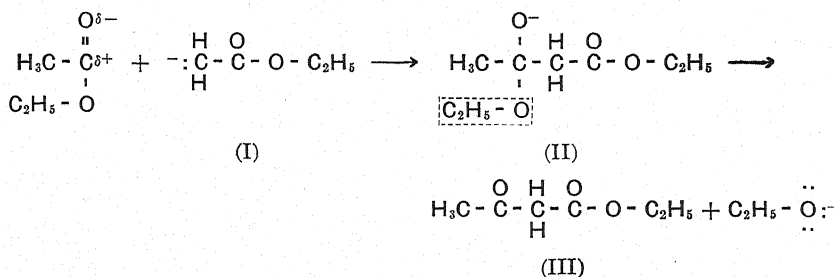
¹ Note that these groups, even when alike, must be introduced in the two successive stages described.

or less competitive and, in general, better yields of ketones are obtained. The malonic ester synthesis (Sec. 20-19) is usually preferable to get the desired acids.

20-18 Claisen Condensation. Ethyl acetoacetate is prepared and manufactured from ethyl acetate by condensing two molecules with the aid of a catalyst such as ethoxide ion. Initially, the catalyst withdraws a proton from the α carbon (CH_3 group) of a molecule of ethyl acetate:



The anion (I) adds at the $+\delta$ carbonyl carbon of a second molecule of ethyl acetate to give (II):

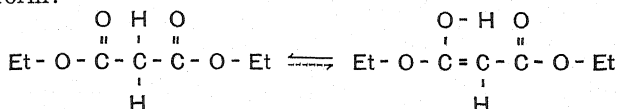


(II) loses ethoxide ion, thus restoring the catalyst and forming (potentially) the desired product, ethyl acetoacetate (III). Actually, in the alkaline solution, ethyl acetoacetate exists as the resonating anion of its sodium derivative. At the end of the reaction sulfuric acid is added to liberate the free ester.

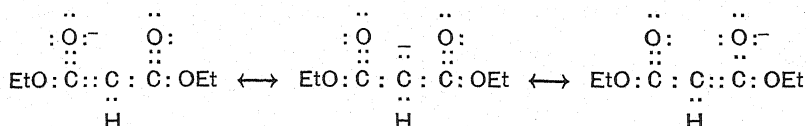
This is an example of the *Claisen condensation*, a reaction which can be used with any ester which has two hydrogen atoms on the *alpha* carbon. It may be applied both to self-condensations, as just illustrated, and to condensations with certain aldehydes and ketones. Sodamide, NaNH_2 , or another strongly nucleophilic substance can be used instead of ethoxide ion as the catalyst.

20-19 Malonic Ester Synthesis. The preparation of diethyl malonate, commonly called *malonic ester*, was described in Section 19-4. The substance is a colorless liquid (b.p. 198.9°C) which is very sparingly soluble in water. Solubility is not increased in the presence of alkalies, and ordinary specimens give no ferric chloride coloration and do not react with bromine. These facts point to its existence as the pure keto form. But it does dissolve sodium, and when the salt is acidified and tested *immediately*, both the bromine-addition and ferric chloride tests are positive. It appears, therefore, that malonic ester is a tautomeric compound

like ethyl acetoacetate but that equilibrium lies close to 100 per cent of the keto form:



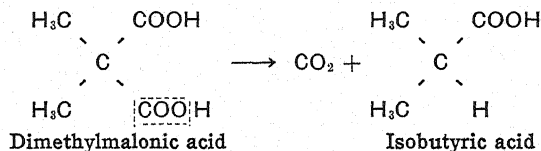
When 1 gram-atomic weight of sodium is dissolved by a mole of malonic ester, the resulting organic anion has a hybrid structure to which all three of the following forms contribute:



Alkyl halides react with this anion, in the same way that they do with that of ethyl acetoacetate, to form *C*-alkyl derivatives (I). By repetition of the reactions with sodium and alkyl halide, dialkyl derivatives (II) are obtained:



These esters can be saponified to substituted malonic acids of the types $\text{RHC}(\text{COOH})_2$ and $\text{RR}_1\text{C}(\text{COOH})_2$, in which two carboxyl groups are attached to the *same* carbon atom. Hence, as with the parent malonic acid, a molecule of CO_2 is eliminated on heating, *e.g.*,

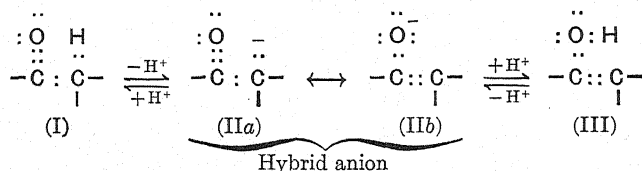


By choosing the alkyl radicals¹ for introduction into malonic ester it is possible to prepare in this way many monocarboxylic acids. The method is especially useful for obtaining acids with chains forked at the *alpha* carbon. An important industrial use of the substituted malonic acids and their esters is their condensation with urea in manufacturing hypnotic drugs of the barbitol family (Sec. 19-14).

20-20 Reactions through Enolizations. Quite a number of base-

¹ The low reactivity of aryl halides does not permit the introduction of phenyl groups in this way. Phenylmalonic ester, required for the manufacture of phenobarbital, can be made from phenylacetic acid by reaction with ethyl oxalate or with ethyl carbonate.

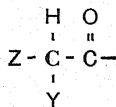
catalyzed chemical changes¹ which appear unconnected are actually related closely. The intermediate common to all of them is a hybrid anion of the nature of (II) in the system already outlined in Section 20-14 and here repeated:



Such an anion can be formed with the aid of a base from molecules in which a sufficiently acidic hydrogen atom is attached to carbon. This requirement is usually met by a hydrogen atom *alpha* to the C=O group in ketones, esters, nitriles, the salts of carboxylic acids, etc. The carbonyl group may be replaced by another strongly electron-attracting group such as CN or NO₂ (Sec. 20-21).

It has been shown in this chapter that keto-enol tautomerism and the alkylations of ethyl acetoacetate and malonic ester proceed through a hybrid anion. The same is true of the aldol condensation (Sec. 10-9) and the Perkin synthesis (Sec. 15-22) and the related reactions described below. At a time when this mechanism was less clearly understood, these were commonly described as due to "enolizations." This term is still widely used although we know now that the formation of enol molecules is not essential when the reactions are base-catalyzed.¹

1. *Racemizations.* Compounds of the general structure



in which the α carbon is asymmetric are easily racemized by bases. Loss of the proton leaves this carbon atom with only three groups attached, and these can assume a planar configuration in the anion (Sec. 17-10). A proton may add either on one side of this plane or on the other, forming equal numbers of D and L molecules.

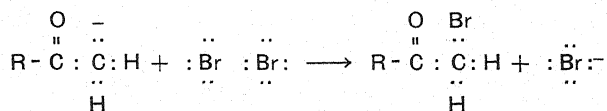
2. *Deuterium uptake* is a characteristic reaction of ketones and other compounds containing the grouping (I). The way in which it occurs, through addition of a deuterium from the solution to a hybrid anion (II), has already been indicated. It is interesting to note that the rates at

¹The present discussion is being restricted to *base-catalyzed* reactions. Some of the changes referred to are also catalyzed by acids, in which case enol molecules must be formed as outlined in Section 20-14.

which certain compounds racemize and take up deuterium are substantially identical, thus showing that the *rate-determining* step¹ in both processes is the same. This is the rate at which the hybrid ion is formed.

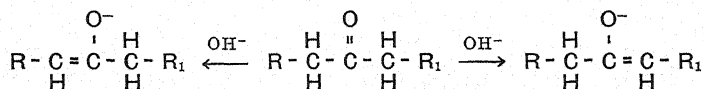
3. *Halogenation of Ketones.* The ease with which halogens substitute α hydrogen atoms of ketones in the presence of alkali was noted in describing the haloform reaction (Sec. 15·10). Careful studies have shown that the rate of substitution is independent of the concentration of halogen and is the same for chlorine, bromine, and iodine. But the rate is directly proportional to the concentration of the alkaline catalyst, hydroxide ion. This leads to the conclusion that here again the rate-determining step is the relatively slow formation of the anion (II), which reacts *as fast as it is formed* with *any* halogen present.

This likewise explains why methyl ketones usually give only *trisubstitution* products. As soon as one halogen atom has entered by the reaction



its attraction for electrons makes the bromomethyl carbon more electro-positive than that of a methyl group. Hence a second—and a third—proton can be removed by the catalyst more easily and faster than the first.

4. *Oxidation of Ketones.* Acetone is stable toward acid oxidants except under forcing conditions but is readily oxidized by a cold *alkaline* solution of potassium permanganate (which is reduced to the green manganate ion, MnO_4^-). This may be regarded as a natural reaction of the hybrid anion, acting as the enolate form (IIb). The variety of products obtained when an unsymmetrical ketone is oxidized (Sec. 10·12) may be due to enolization on *either side* of the carbonyl group:



5. *Alkylation of Ketones.* Sodamide, NaNH_2 , is a powerful base which acts in many ways like sodium. If acetone is treated with sodamide and then with CH_3I , a hydrogen atom is replaced by CH_3 . This *Haller-Bauer*

¹ Suppose A is converted into E through a series of reactions, the rates of which are r_1, r_2 , etc.:

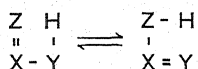


No matter how rapid some of these steps may be, the rate of the over-all change must depend solely on the "bottleneck" caused by the slowest one. The latter, then, is the *rate-determining* step.

reaction can be repeated until all six hydrogen atoms have been replaced, forming $(\text{CH}_3)_3\text{C}.\text{CO}.\text{C}(\text{CCH}_3)_3$. Sodamide withdraws a proton from acetone, and the resulting anion reacts with an alkyl halide as in the acetoacetic ester and malonic ester syntheses.

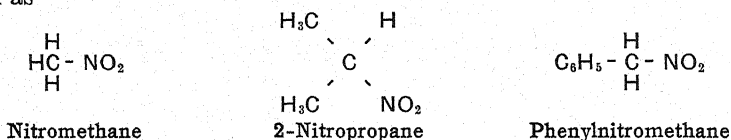
20-21 Generalized Tautomeric Change. Compounds of other types give evidences of tautomerism analogous to that between keto and enol molecules. Occasionally two forms can be isolated. More commonly, only one parent substance is known, but this gives derivatives which indicate its ability to *react as though* it has two structures.

A generalized picture which covers many tautomeric changes is given by the scheme

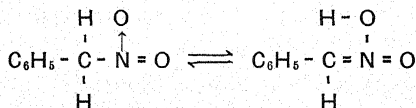


in which X, Y, and Z may represent suitable combinations of carbon, oxygen, sulfur, and nitrogen atoms. Any such system is capable of base-catalyzed tautomerism if the hydrogen atom is acidic enough to be removed by the catalyst. A specific example follows.

Tautomeric Nitro Compounds. Tertiary nitro compounds such as $(\text{CH}_3)_3\text{C}.\text{NO}_2$, including $\text{C}_6\text{H}_5.\text{NO}_2$ and other nitroaromatics, are no more soluble in alkalis than in water, thus indicating the absence of acidic properties. On the contrary, *primary* and *secondary* nitro compounds such as



dissolve *slowly* in alkalis. These substances as ordinarily obtained give no coloration with ferric chloride and react only slowly with bromine. But if their solutions in alkalis are cautiously acidified and tested promptly, they give an intense red color with ferric chloride and combine instantly with bromine. This is part of the evidence for tautomerism. Phenylnitromethane is one such compound of which both forms are known:



Phenylnitromethane

Normal form; a liquid, stable when heated; b.p. 227°; gives no immediate coloration with FeCl_3 ; dissolves *very slowly* in alkali solutions.

Acid-form; crystalline solid; m.p. 84°; passes into the normal form when heated; gives an immediate color with FeCl_3 ; *quickly* dissolves in alkali solutions.

Tautomeric changes between normal and *aci*-nitro compounds seem to proceed through the same steps described in Section 20-14. They are catalyzed by acids and by bases and, when they occur in the presence of D_2O , deuterium enters the organic molecule to form compounds of the type $R.CHD.NO_2$.

Questions

1. In terms of the type formula $R.COOH$ for a simple carboxylic acid, distinguish between "acid derivatives" and "substituted acids."

2. State and illustrate the essential differences between the two methods used to indicate positions when naming substituted acids.

3. (a) Explain how α - and β -halogen-substituted acids can be made from saturated and unsaturated simple acids, respectively. (b) Write structural equations for the full series of reactions involved in preparing α -chloropropionic acid from lactic acid. (c) Suggest a method for the preparation of chloroacetic acid from ethylene chlorohydrin.

4. Write full structural equations for all reactions involved in the conversion of: (a) $CH_2Cl.COOH$ into $CH_2NH_2.COOH$; (b) $CH_3.CHCl.COOH$ into $CH_3.CHOH.COOH$; (c) $CH_3.CHCl.CH_2.COOH$ into $CH_3.CH:CH.COOH$; (d) $CH_2Cl.COOH$ into $CH_2Cl.COCl$; (e) $CH_2Cl.COOH$ into $CH_2Cl.CONH_2$; (f) $CH_2Cl.COOH$ into $HOOC.CH_2.COOH$; (g) $CH_2Cl.COOH$ into 2,4-D.

5. (a) Summarize the effects of halogen in the radical R of $R.COOH$ upon the ionization of the $COOH$ group, in terms of the nature, the position, and the number of halogen atoms. (b) Explain these effects.

6. Name four types of compounds, already containing the carboxyl group, from which hydroxy acids are readily prepared; give one specific example of each, with equations.

7. (a) Write the equations involved in the preparation of mandelic acid, $C_6H_5-CHOH.COOH$, from benzaldehyde. (b) Explain why this method is limited to the preparation of α -hydroxy acids. (c) Explain why the mandelic acid obtained by the cyanohydrin synthesis is racemic. (d) Write the formulas of two hydroxy acids which do not contain an asymmetric atom.

8. In terms of their relations to simple compounds give reasons for expecting: (a) that only the alcoholic group in lactic acid will be affected by mild oxidation; (b) that only the carboxyl hydrogen will be replaced when the acid is treated with cold milk of lime; (c) that PCl_5 will react with lactic acid at two points; (d) that one halogen atom in α -chloropropionyl chloride will be hydrolyzed much more readily than the other.

9. What reagents would you use with a hydroxy acid if you desired to esterify (a) the carboxyl group; (b) the hydroxyl group? Give equations.

10. Ethyl lactate boils at $154^\circ C$ and is miscible with water in all proportions. Ethyl propionate boils at $99.1^\circ C$, and 100 ml of water dissolve only 2.4 grams at $20^\circ C$. Account for these differences in properties.

11. (a) Write the structural equation for the condensation of lactic acid to lactide. (b) Write equations showing other ways in which, conceivably, water might be eliminated between molecules of lactic acid. (c) Account for the formation of the compound $HOOC.CH_2.O.CH_2.COOH$, along with $CH_2OH.COOH$, when chloroacetic acid is boiled with an alkali. (d) Would you expect to be able to obtain the mixed anhydride $CH_3.CHOH.CO.O.CO.CH_3$ by treating sodium lactate with acetyl chloride? Why?

12. (a) What are lactones and from what types of hydroxy acids are they formed? (b) What structural relation is there between the dicarboxylic acids that yield cyclic anhydrides and the hydroxy acids that yield lactones?

13. Discuss the chemistry and uses of Fehling's solution.

14. Give in detail the evidence that shows: (a) that the chemical properties of ordinary ethyl acetoacetate cannot be explained in terms of any single structural formula; (b) that the compounds described as the keto and enol forms are mutually convertible.

15. (a) When a drop of ferric chloride solution is added to a solution of ethyl acetoacetate in dilute alcohol, the initial red color becomes more intense on standing; explain fully. (b) Explain why ethyl acetoacetate is more soluble in dilute sodium hydroxide than in water. (c) Write equations for the reactions that account for the evolution of hydrogen when dry acetone is treated with metallic sodium.

16. Explain in detail, with all essential formulas, the mechanism of keto-enol tautomerism and the role of an alkaline catalyst.

17. Explain the stabilization of enols through chelation.

18. Give the essential steps and reactions involved in the Kurt Meyer method for determining the enol content of keto-enol tautomers.

19. (a) Starting with acetoacetic ester (keto form), give the full set of reactions involved in introducing one ethyl group. (b) Starting with the product of (a), give the full set of reactions involved in introducing a normal butyl radical. (c) Write equations for the ketone and acid decompositions, giving reagents, of the products of (a) and of (b).

20. Show *what* radicals it would be necessary to introduce into acetoacetic ester so that, by the ketone or the acid decomposition, the following compounds could be obtained: (a) $\text{CH}_3\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CH}_3$; (b) $(\text{C}_2\text{H}_5)_2\text{CH}\cdot\text{COOH}$; (c) *n*-hexanoic acid; (d) methyl isopropyl ketone.

21. Write: (a) equations for the synthesis of malonic ester from chloroacetic acid; (b) resonance formulas for the hybrid organic ion of sodium diethyl malonate; (c) type formulas for the mono- and dialkyl derivatives of malonic ester.

22. Write equations for: (a) all steps in the conversion of malonic ester into its monobutyl derivative; (b) converting the product of (a) into ethylbutylmalonic ester; (c) the reactions which occur when the products of (a) and (b) are hydrolyzed and strongly heated; (d) the condensation between diethylmalonic ester and urea in the presence of sodium ethoxide (Sec. 19-14).

23. Indicate what radicals it would be necessary to introduce into malonic ester in order to obtain: (a) *n*-butyric acid; (b) isobutyric acid; (c) *n*-heptanoic acid; (d) $(\text{C}_3\text{H}_7)_2\text{CH}\cdot\text{COOH}$.

24. Review the aldol condensation (Sec. 10-9) and the haloform reaction (Sec. 15-10) in connection with the additional information supplied in this chapter.

25. (a) Write the structural formulas of two carbonyl compounds which are incapable of tautomeric change. (b) Show how the tautomerism of normal and *aci*-nitro compounds resembles and differs from keto-enol tautomerism. (c) Explain why nitrobenzene is not a tautomeric substance.

CHAPTER 21

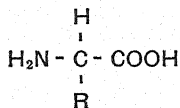
AMINO ACIDS AND PROTEINS

The aliphatic amino acids of major interest are those which occur in the important plant and animal products called proteins. Hence this class of substituted acids was merely mentioned in the last chapter and deferred for study here in connection with the proteins.

AMINO ACIDS

21.1 Structure and Classification. Some 50 different amino acids are claimed to have been isolated from one or more proteins, but the evidence concerning some of these needs confirmation. The names and formulas of the 20 which occur most regularly are given in Table 21.1. Since many of the systematic names are cumbersome, these biologically important amino acids are usually referred to by the names printed in *italics* in this table.

The natural amino acids all resemble each other in that an amino group¹ is attached to an *alpha* carbon atom. Hence they contain the common grouping

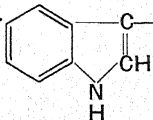


Significant differences in the nature of R lead to a subdivision into three classes, shown in Table 21.1. The α -amino acids of class (I)—which is the largest—contain only one acid and one basic group. In class (II) the radical R contains a second COOH group, making two in the molecule. In class (III) R contains a second amino (or other basic, nitrogenous) group. Some consequences of these differences in structure will be mentioned later.

¹ Proline and hydroxyproline are exceptions. These likewise have a nitrogen atom attached to the α carbon, but it is part of a heterocyclic ring and not in a simple NH₂ group.

TABLE 21-1 PRINCIPAL AMINO ACIDS ISOLATED FROM PROTEINS

I. Monoaminomonocarboxylic acids:

<i>Glycine</i>	$\text{CH}_2\text{NH}_2\text{COOH}$ Aminoacetic acid
<i>Alanine</i>	$\text{CH}_3\text{CHNH}_2\text{COOH}$ α -Aminopropionic acid
<i>Serine</i>	$\text{CH}_2\text{OHCHNH}_2\text{COOH}$ β -Hydroxy- α -aminopropionic acid
<i>Phenylalanine</i>	$\text{C}_6\text{H}_5\text{CH}_2\text{CHNH}_2\text{COOH}$ β -Phenyl- α -aminopropionic acid
<i>Tyrosine</i>	$\text{HOC}_6\text{H}_4\text{CH}_2\text{CHNH}_2\text{COOH}$ β -Parahydroxyphenyl- α -aminopropionic acid
<i>Cystine</i>	$\text{SCH}_2\text{CHNH}_2\text{COOH}$ 1 $\text{SCH}_2\text{CHNH}_2\text{COOH}$ β , β' -Dithiodialanine
<i>Methionine</i>	$\text{H}_3\text{CSCH}_2\text{CH}_2\text{CHNH}_2\text{COOH}$ γ -Methylmercapto- α -aminobutyric acid
<i>Threonine</i>	$\text{CH}_3\text{CHOHCHNH}_2\text{COOH}$ β -Hydroxy- α -aminobutyric acid
<i>Valine</i>	$(\text{CH}_3)_2\text{CHCHNH}_2\text{COOH}$ α -Aminoisovaleric acid
<i>Leucine</i>	$(\text{CH}_3)_2\text{CHCH}_2\text{CHNH}_2\text{COOH}$ α -Aminoisocaproic acid
<i>Isoleucine</i>	$\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)\text{CHNH}_2\text{COOH}$ α -Amino- β -methylvaleric acid
<i>Proline</i>	$ \begin{array}{c} \text{H}_2\text{C} \quad \text{CH}_2 \\ \quad \quad \\ \text{H}_2\text{C} \quad \quad \text{CH.COOH} \\ \diagdown \quad \diagup \\ \text{N} \\ \\ \text{H} \end{array} $ 2-Pyrrolidinecarboxylic acid
<i>Hydroxyproline</i>	$ \begin{array}{c} \text{HO.HC} \quad \text{CH}_2 \\ \quad \quad \\ \text{H}_2\text{C} \quad \quad \text{CH.COOH} \\ \diagdown \quad \diagup \\ \text{N} \\ \\ \text{H} \end{array} $ 4-Hydroxy-2-pyrrolidinecarboxylic acid
<i>Tryptophane</i>	 $\text{CH}_2\text{CHNH}_2\text{COOH}$ α -Amino-3-indolepropionic acid

II. Monoaminodicarboxylic acids:

<i>Aspartic acid</i>	$\text{HOOCCH}_2\text{CHNH}_2\text{COOH}$ Aminosuccinic acid
<i>Glutamic acid</i>	$\text{HOOCCH}_2\text{CH}_2\text{CHNH}_2\text{COOH}$ α -Aminoglutaric acid

TABLE 21.1 (Continued)

Hydroxyglutamic acid..... $\text{HOOC} \cdot \text{CH}_2 \cdot \text{CHOH} \cdot \text{CHNH}_2 \cdot \text{COOH}$
 α -Amino- β -hydroxyglutaric acid

III. Diaminomonomocarboxylic acids:

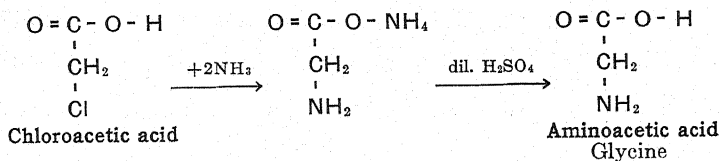
Lysine..... $\text{CH}_2\text{NH}_2 \cdot (\text{CH}_2)_3 \cdot \text{CHNH}_2 \cdot \text{COOH}$
 α, ϵ -Diaminocaproic acid

Arginine..... $\begin{array}{c} \text{NH}_2 \\ | \\ \text{HN}=\text{C} \cdot \text{NH} \cdot (\text{CH}_2)_3 \cdot \text{CHNH}_2 \cdot \text{COOH} \end{array}$
 α -Amino- δ -guanidovaleric acid

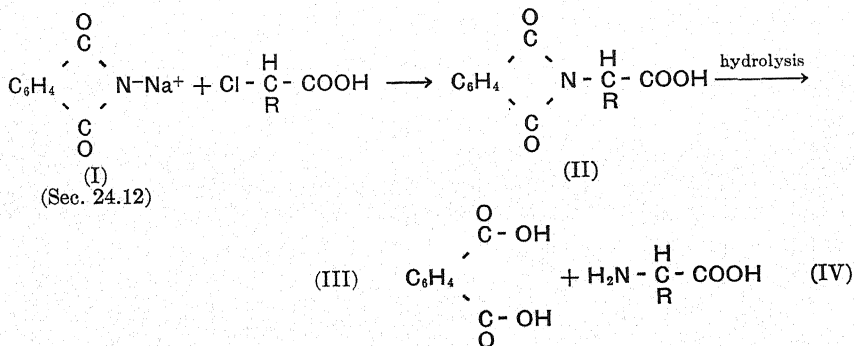
Histidine..... $\begin{array}{c} \text{HC}=\text{C} \cdot \text{CH}_2 \cdot \text{CHNH}_2 \cdot \text{COOH} \\ | \quad | \\ \text{N} \quad \text{NH} \\ \diagdown \quad / \\ \text{C} \\ | \\ \text{H} \end{array}$
 α -Amino- β -imidazolepropionic acid

21.2 Synthesis. The structures of the naturally occurring amino acids have been established, like those of organic molecules in general, by synthesis from related compounds of known structures. Among the more important general methods are the following:

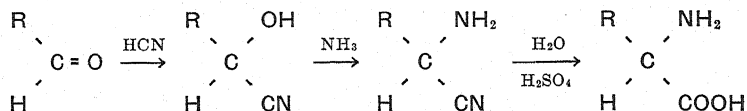
From α -halogen-substituted acids by replacing the halogen atom by the NH_2 group. This may be accomplished, as in an alkyl halide, by reaction with a large excess of strong ammonia, *e.g.*,



Better results are often obtained by the Gabriel synthesis, in which the halogen-substituted acid is reacted with sodium phthalimide (I) to give a product having structure (II). On hydrolysis this yields phthalic acid (III), or its salt, and an amino acid (IV):



From aldehydes and ketones through their cyanohydrins. For this synthesis the cyanohydrin is treated with strong ammonia, whereby the OH group is replaced by NH_2 (Strecker reaction). The CN group is then hydrolyzed to COOH in the usual way; e.g.,



21-3 Amino Acids as Dipolar Ions. The amino acids obtained from protein hydrolysis are all crystalline solids. They melt only at high temperatures, usually around 300°C or above, and probably always with decomposition. Such melting points show that the molecules are bound together in the crystal lattices by forces much stronger than those in typical organic crystals; they suggest on the contrary the powerful electrostatic attractions which exist in ionic crystals (Sec. 1-3). The density of glycine (1.60), which is exceptionally high for an organic compound containing no heavy atoms, likewise indicates very close packing in the crystals. Glycine and many other of the amino acids, though not all of them, are quite freely soluble in water; but all are practically insoluble in absolute alcohol, ether, benzene, and other liquids which are good solvents for most organic compounds. This resemblance in solubility relations to the ionic crystals of inorganic salts is a further suggestion of electrical charges.

The properties just described are part of the evidence which has forced the conclusion that the natural amino acids have a structure fundamentally different from any classes of organic compounds previously studied. We can no longer regard them as (I) but rather as *dipolar ions*—sometimes called *zwitterions*—pictured by (II):



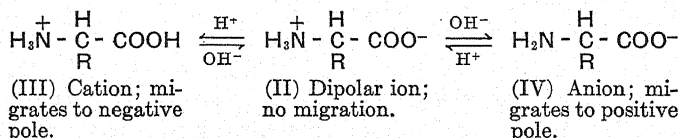
The latter represents a species of inner salt in which a proton lost by the COOH group (acting as in acetic acid) is taken up by the NH_2 group (acting as in ethyl amine). Thus both groups acquire *unit* electrical charges. Such a dipolar structure explains the properties of α -amino acids described above and below.

21-4 Dipole moments of amino acids cannot be determined by the methods used for other organic compounds, but indirect methods indicate that they are very high. Thus, instead of values of the order of 2 to 3 D commonly encountered, it is estimated that the dipole moment of glycine is approximately 15 D. This is in close agreement with the value cal-

culated on theoretical grounds (cf. Sec. 1·10). For any α -amino acid having the dipolar structure indicated above the difference in charge is that of one electron, 4.8×10^{-18} esu. X-ray measurements on glycine crystals give a distance of 2.96 Å between the center of the plus charge, on the nitrogen atom, and the center of the minus charge—taken as midway between the two oxygen atoms of the carboxylate group. Multiplying 4.8×10^{-18} by 2.96 gives 14.2×10^{-18} esu = 14.2 D. Amino acids in which the charges are separated by greater distances (*e.g.*, ϵ -aminocaproic acid) apparently have dipole moments three to four times that of glycine.

21·5 Isoelectric Point. The dipolar-ion structure explains the rather surprising fact that the direction of migration¹ of amino acids in an electrical field depends upon the hydrogen-ion concentration of the solution. In solutions of relatively high acidity, *e.g.*, pH 1, prepared by dissolving glycine in hydrochloric acid, the amino acid migrates toward a negative electrode, showing that it carries a positive charge. In alkaline solutions, *e.g.*, at pH 9, glycine migrates toward a positive electrode like any ion carrying a negative charge. At the intermediate concentration of pH 5.97, *glycine does not migrate* in an electrical field. The pH corresponding to this state of no migration is known as the *isoelectric point*.

The evidence is strong that at pH 5.97 glycine exists entirely (or almost entirely) as the dipolar ion, which is unable to migrate because it is attracted equally in both directions. Addition of hydrochloric acid causes progressive addition of protons to the COO^- groups, thus neutralizing the minus charge and forming simple cations like (III). Starting again at the isoelectric point and adding an alkali, we bring about the removal of protons from the NH_3^+ groups (compare the action of strong alkali on ammonium ion and amine cations) and formation of the anion (IV):

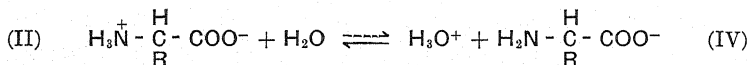


All the aliphatic amino acids containing only one acidic and one basic group have isoelectric points in the vicinity of pH 6. For those containing two acidic groups this value is around pH 3, while the amino acids con-

¹ It should be recalled that if electrodes carrying direct current are placed in the water solution of a typical salt such as Na^+Cl^- , any negative ion (anion) will migrate toward the positive electrode and any positively charged ion (cation) toward the negative electrode. Using a suitable U-shaped apparatus, the slow migration of colored ions such as MnO_4^- and $\text{Cu}(\text{H}_2\text{O})_4^{++}$ can be followed by the eye. Other methods are available for following the movement of colorless ions.

taining two basic groups have their isoelectric points on the alkaline side, *e.g.*, pH 9.74 for lysine.

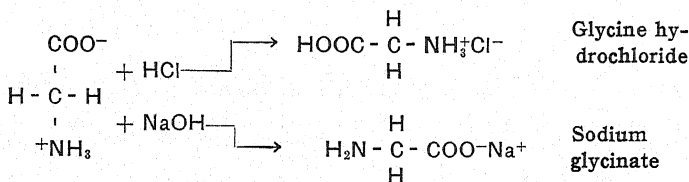
It may be asked why the isoelectric point of glycine lies at pH 5.97 instead of at neutrality, pH 7. This is because the H_3N^+ ends have a somewhat greater tendency to lose protons than have the COO^- ends to gain them. In other words, when glycine crystals are dissolved in distilled water, the following reaction proceeds toward the right to a slight extent:



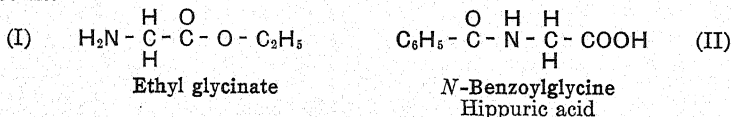
This is reversed and the small amount of the anion (IV) converted back into dipolar ions by adding the minute quantity of HCl necessary to make the pH of the solution 5.97.

21.6 Chemical Properties. The amino acids enter, under appropriate conditions, into the various reactions of the simple carboxylic acids and the primary alkyl amines. It suffices to mention:

Salt Formation. Amino acids form salts both with acids and with bases, as would be predicted from the dipolar-ion structure. These salts are often quite soluble in water but can be precipitated at suitable concentrations from acid and alkaline solutions, respectively, *e.g.*,



Esterification. Amino acids are converted into their esters by reaction with alcohols in the presence of at least one equivalent of a mineral acid; *e.g.*, with ethyl alcohol, glycine yields ethyl glycinate (I). The mineral acid is needed to convert the COO^- groups of the dipolar ions into the COOH groups which are necessary for the esterification reaction. Esters of amino acids can be distilled under reduced pressure, a property which has been utilized in separating the mixtures obtained by the hydrolysis of proteins.

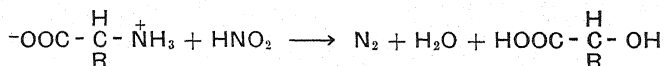


Acylation. The NH_2 groups in amino acids, like those in primary amines, react with acid halides to yield *N*-acyl derivatives; *e.g.*, glycine reacts with benzoyl chloride in the presence of sodium hydroxide to form *N*-benzoyl glycine (II). It is interesting to note that most animals

render harmless any benzoic acid taken into the body by combining it with glycine and excreting benzoylglycine in the urine. This is an example of the protective mechanism called *detoxification*.

Formol Titration. If the solution of a pure amino acid is titrated with sodium hydroxide in the ordinary way, any indicator will show alkalinity long before one equivalent of base has been added. This difficulty is overcome in the method known as formol titration, devised by Sørensen, in which an excess of a neutral solution of formaldehyde is first added to the solution to be titrated. Formaldehyde reacts with the NH_2 group in a way¹ which destroys its ability to bind protons and thus makes possible titration of the COOH group with just as much accuracy as in acetic acid. This method of "formol" titration is used in estimating carboxyl groups in proteins and their products of hydrolysis.

Determination of Amino Nitrogen. When treated with excess of acetic acid and sodium nitrite, the NH_2 groups in amino acids react to liberate nitrogen quantitatively:

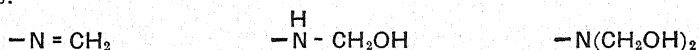


The determination is made in a special piece of apparatus, devised by Van Slyke, in which the evolved nitrogen gas is collected, washed free of impurities, and its volume measured accurately at known temperature and pressure. This procedure has been found of great value in estimating the number of primary amino groups present in proteins and their products of hydrolysis.

21.7 Configuration. In every α -amino acid except glycine the *alpha* carbon has four different atoms and groups attached and is therefore asymmetric. Hence, each of these acids is capable of existing as either of two mirror-image isomers. It appears, however, that only one form of any amino acid ever occurs in the proteins. For example, when any protein is hydrolyzed by acids or enzymes,² the valine isolated is always dextro- and the cystine levorotatory.

There is now much evidence that—regardless of the observed direction

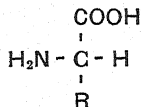
¹ The mode of reaction between CH_2O and NH_2 groups is not entirely clear. The following have been suggested as probable types of linkages in the reaction product or products:



The essential point is that the nitrogen atom is no longer basic.

² When proteins are hydrolyzed by alkalis, amino acids are racemized and obtained as DL mixtures. Synthetic methods likewise yield optically inactive mixtures; these are usually resolved by acetylating the NH_2 group and fractionally crystallizing the salts formed with some optically active base.

of rotation—all the natural α -amino acids belong to the L series (Sec. 17-9). That is, the COOH, H, R, and NH_2 on the α carbon are arranged clockwise in the common projection formula:



Hence it is becoming customary to use the letter L before the name of every natural amino acid (except inactive glycine) and to indicate the direction of rotation by the usual signs, e.g., L-(+)-valine, L-(−)-cystine.

PROTEINS

The jellylike *protoplasm* which is the essential component of all living cells consists mainly—aside from water—of complex organic compounds of nitrogen. Early recognition by Mulder (1838) of the importance of this nitrogenous material to living matter led to the name *protein*, from the Greek *proteios*, meaning *to take the first place*. Later investigations showed that all protein is not identical, and we now use the plural form *proteins* to describe many different but closely allied products of plant and animal life.

21-8 Molecular Composition. Proteins differ from the fats and carbohydrates by containing nitrogen—on the average, close to 16 per cent.¹ They usually contain sulfur and frequently phosphorus, in amounts ranging from traces up to 3 or 4 per cent. Other elements are found in certain special proteins, such as iron in hemoglobin and iodine in the thyroid proteins.

The molecular weights of proteins cannot be determined with high precision, but all methods point to very large molecules. Values below 20,000 are rare; zein (from corn), pepsin, and insulin have molecular weights of the order of 35,000 to 40,000; hemoglobin and one of the serum proteins are around 65,000 to 70,000; the enzyme urease shows a value of about 480,000; for certain viruses, such as that of the tobacco-plant mosaic disease, apparent molecular weights of 10 to 50 millions have been reported.

What such numbers mean in terms of molecular complexity is best indicated by a specific example. If the molecular weight of casein is taken at 32,000—and some much higher values have been reported—its molecular formula is, approximately, $\text{C}_{1416}\text{H}_{2260}\text{N}_{360}\text{O}_{448}\text{S}_8\text{P}_8$!

21-9 Hydrolysis of the proteins with the aid of acids, alkalies, and

¹ The usual method for estimating protein in foods, feed stuffs, and fertilizers is to determine the *total nitrogen* percentage by a suitable analytical method and multiply the result by 6.25 to report the percentage of protein ($6.25 = \frac{100}{16}$).

enzymes has furnished the most important evidence as to their structure (Sec. 21-10). Such hydrolytic cleavages of the huge protein molecule yield progressively simpler substances known, in the order of decreasing complexity, as proteoses, peptones, and peptides. Ultimately, all these are further hydrolyzed to mixtures of α -amino acids. The latter are the "building blocks" from which protein molecules are constructed. The differences between individual proteins lie in the *nature*, the *number*, and the *arrangement* of these structural units.

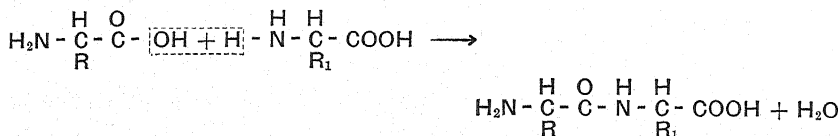
Table 21-2 illustrates how widely the content of individual amino acids may vary in different proteins. Some, like the casein of milk, contain all 20 of the acids listed. But in others the most careful work has failed to detect certain ones, *e.g.*, gelatin contains no tryptophane or tyrosine. Silk fibroin is unusual in that only four different amino acids make up more than 90 per cent of its molecule.

TABLE 21-2 AMINO-ACID DISTRIBUTION IN TYPICAL PROTEINS†
(In per cent)

Amino acid	Egg albumin	Insulin	Zein	Casein	Gelatin	Silk fibroin
Glycine.....	0.0	0.45	25.5	43.8
Alanine.....	2.22	9.79	1.85	8.70	26.4
Serine.....	3.57	1.02	5.0	3.3	13.57
Threonine.....	2.66	3.5	1.4	1.36
Valine.....	2.50	1.88	7.93	0.0	
Leucine and Isoleucine....	10.71	30.00	25.00	9.70	7.10	2.50
Proline.....	4.15	9.04	8.70	19.7	1.00
Oxyproline.....	0.08	0.23	14.4	
Phenylalanine.....	5.07	7.6	3.88	1.40	1.50
Methionine.....	5.23	2.35	3.25	2.59
Cystine.....	1.78	12.50	0.91	0.42	0.17	
Tryptophane.....	1.18	1.54	0.0	
Tyrosine.....	3.97	12.5	5.90	5.36	0.0	13.2
Histidine.....	1.48	10.7	0.82	2.50	2.94	0.07
Arginine.....	5.66	3.05	1.60	3.72	8.68	0.76
Lysine.....	4.97	1.26	0.0	6.25	5.92	0.25
Aspartic acid.....	8.1	1.8	5.95	3.40	
Glutamic acid.....	16.1	30.00	31.30	21.6	5.80	
Hydroxyglutamic acid....	1.36	2.50	10.5	0.0	
Ammonia.....	1.23	1.65	3.64	1.61	0.40	
Total.....	75.71	107.89	105.95	103.94	108.81	107.0

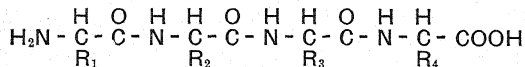
† From Cohn and Edsall, "Proteins, Amino Acids, and Peptides," Reinhold Publishing Corporation, New York, 1943. Reproduced through the courtesy of the authors and publishers.

21.10 Protein Structure. All the evidence leads to the conclusion that *proteins are compounds in which many α -amino acid molecules are united through peptide linkages.* This is the linkage formed by the elimination of water between the COOH group of one α -amino acid and the NH_2 group of another, as indicated by the type equation



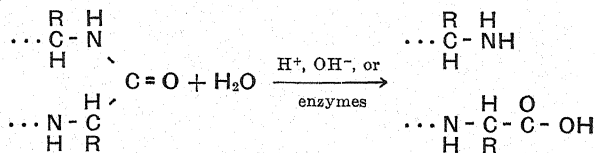
The direct reaction here indicated *cannot* be brought about in the laboratory; just how living organisms accomplish it is unknown.

The relatively simple compounds in which amino acids are thus united by the peptide linkage are called peptides—*di*-, *tri*-, *tetra*-, etc., or, collectively, *polypeptides*. The formula for a typical tetrapeptide is



in which R_1 , R_2 , R_3 , and R_4 may represent the same or different groups.

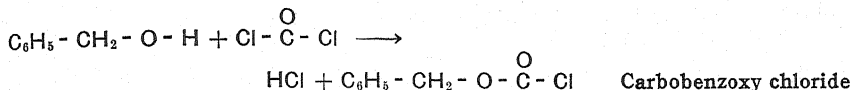
The following is part of the evidence for the peptide structure of proteins. When a protein is subjected to slow hydrolysis, it can be shown by suitable analytical methods—*e.g.*, formol titration and the Van Slyke determination—that the numbers of free COOH and NH_2 groups *increase equally*. This is the result to be expected if the hydrolysis of proteins, proteoses, peptones, etc., consists in the cleavage of peptide linkages after the fashion



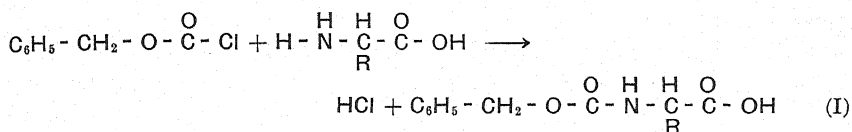
Further evidence has been obtained through synthesis. By methods such as that described below it has been possible to build up peptides of known structure in which as many as 18 and 19 amino-acid molecules are combined in a chain through peptide linkages. Both the physical and chemical properties of these synthetic polypeptides resemble closely those of protein fragments of about the same size isolated as intermediate products of hydrolysis.

21.11 Peptide Synthesis. As already stated, peptides cannot be prepared in the laboratory by direct reaction between molecules of amino acids. The various indirect methods which have been used may be

illustrated by one of the more recent and most effective syntheses, known as *Bergmann's carbobenzoxy method*. The reagent, carbobenzoxy chloride, is prepared by treating benzyl alcohol with carbonyl chloride in toluene:



This acid chloride reacts with an amino acid to give a product (I) in which the amino group is protected against attack by the further reagents which will have to be used:



The COOH group in (I) can now be converted into COCl by the usual methods, such as the action of thionyl chloride, and the resulting acid chloride allowed to react with the NH₂ group of another amino-acid molecule; thus a peptide linkage is established. This sequence of reactions is repeated as often as desired. Finally, when it is no longer needed, the carbobenzoxy group is replaced by a hydrogen atom by catalytic hydrogenation at room temperature.

21.12 Synthesis of Proteins. The most complex peptide ever synthesized contained 19 amino-acid molecules—15 of one kind and 4 of another—joined by 18 peptide linkages. Its molecular weight of 1326 is large in comparison with most synthetic organic compounds, but the substance still represents only a small fragment of a protein molecule. The average molecular weight of the amino acids is around 125; hence proteins of relatively low molecular weight, say 30,000 to 40,000, must contain some 250 to 300 amino-acid residues in their molecules. When we consider that these acids must be selected in definite numbers from 20 or more varieties, and arranged in a specific order,¹ there seems small probability of duplicating in the laboratory that synthesis of specific proteins which goes on regularly and smoothly in all living cells.

21.13 Protein Classification. Proteins are ordinarily divided into three major classes, as follows:

Simple² proteins are defined as natural compounds which on hydrolysis

¹ The difficulty of the task may be visualized in part by considering that, while the English alphabet contains only 26 letters, our unabridged dictionaries list some 500,000 words formed from them.

² The word *simple* is used in contrast with *conjugated* and *derived*. In view of the tremendous complexity of all proteins and the ordinary meaning of "simple," its selection for use here seems unfortunate.

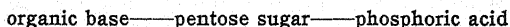
yield α -amino acids with only *small* amounts of other substances, *e.g.*, ammonia. Biochemists and physiologists subdivide these simple proteins—mainly on the basis of solubilities and precipitation relations—into albumins, globulins, glutelins, prolamines, histones, protamines, and albuminoids.

Conjugated proteins are naturally occurring compounds in which a simple protein is linked more or less firmly with a nonprotein *prosthetic* group. They are subdivided according to the nature of this group. In the *glycoproteins*, one of which occurs in saliva, the prosthetic group is a carbohydrate. The blood pigment hemoglobin, which contains red, non-protein hematin joined to a colorless simple protein, is called a *chromo*-protein. *Nucleoproteins* are discussed below.

Derived proteins are products formed from native proteins by chemical changes. Very superficial changes may lead to marked alterations in solubility relations, as observed in the coagulated albumin of a boiled egg. More deep-seated, hydrolytic cleavages yield proteoses, peptones, and peptides as already stated.

21-14 Nucleoproteins exist in all cells and are especially abundant in the nuclei. They are conjugated proteins, of very high molecular weights, in which the prosthetic group is a nucleic acid. This is joined to some simple protein by a linkage which is very easily broken by hydrolysis and appears to be saltlike in nature.

Nucleic Acids. Yeast nucleic acid and thymonucleic acid, from the thymus gland, have been most thoroughly studied. On complete hydrolysis they yield mixtures containing a pentose sugar, phosphoric acid, and several organic bases. *Regulated* hydrolysis of a nucleic acid by acids or enzymes yields a mixture, in roughly equal amounts, of four *nucleotides*. These are compounds of the general structure



Nucleotides differ in the nature of the organic base, which may be derived either from purine or pyrimidine (Sec. 26-12). The sugar is D-ribose or desoxyribose (Sec. 18-13).

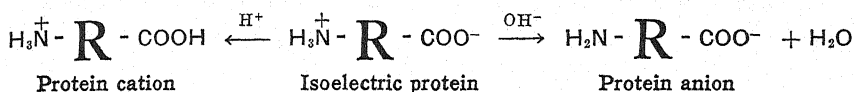
Certain enzymes split phosphoric acid away from a nucleotide. The residue, consisting of the base united with the sugar molecule, is a specific type of glycoside called a *nucleoside*.

21-15 Acid-base Relations. Proteins, like their component amino acids, can combine both with acids and with bases. This is mainly through amino¹ and carboxyl groups not involved in peptide linkages. A protein molecule made up entirely of amino acids of class (I), Table

¹ Along with the simple NH_2 group we must include here the guanidine and imidazole groups of arginine and histidine, respectively, which also bind protons.

21-1, could have only one NH_2 and one COOH group—at the ends of its long chain. Most proteins, however, contain considerable amounts of the acids of classes (II) and (III) and therefore have many side chains which supply acidic and basic groups,¹ respectively.

At its isoelectric point—which may lie between pH 2 and pH 12 and is specific for each kind—a protein must be regarded as a giant multipolar ion with equal numbers of plus and minus charges. Additions of acids and bases produce changes entirely similar to those of an α -amino acid (Sec. 21-5). Using R to represent the main body of the molecule and showing only one each of the acidic and basic groups, this may be pictured as follows:



The properties of proteins in solution are affected greatly by the hydrogen-ion concentration. At their isoelectric points proteins are least soluble, most readily coagulated, and most completely “salted out” by neutral inorganic salts; osmotic pressure, viscosity, and swelling (as of gelatin) are all minimal. Precipitation by the cations of heavy metals, such as cupric and mercuric ions, is most complete on the alkaline side of the isoelectric point, where the protein exists as an anion. Conversely, precipitation by complex anions (such as those of picric, tannic, sulfosalicylic, and phosphotungstic acids) occurs only on the acid side where the protein is positively charged.

21-16 Denaturation; Coagulation; Precipitation. The protein molecule is an unstable structure readily altered by outside influences. *Denaturation* is defined as any change which causes a soluble native protein to become insoluble at its isoelectric point. It appears to involve changes in the orderly structure of the molecule through breaking weak linkages such as hydrogen bonds. The familiar change observed when egg white is cooked is an example. If the protein is in solution, the chemical change of denaturation will be followed by separation of the insoluble denatured protein. This is described somewhat indiscriminately as *precipitation* or *coagulation*. The latter term is preferably reserved for irreversible changes.

Heat Coagulation. Most proteins, though not all, are denatured and coagulated irreversibly by heat. In general this occurs at temperatures well below the boiling point of water and, as already indicated, most readily at the isoelectric point.

¹ See footnote, page 416.

Effects of Alcohol. Many proteins are precipitated from their water solutions by adding 95 per cent ethyl alcohol. If the precipitate is separated from the alcohol promptly, it usually can be redissolved in water; if allowed to stand under alcohol for some time, the change becomes irreversible. This property is applied in the hardening of biological material and in the use of alcohol as a germicide.

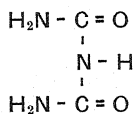
Salting Out. Most proteins can be precipitated by saturating their solutions with readily soluble neutral salts such as magnesium sulfate and ammonium sulfate. This is analogous to the familiar salting out of simpler organic compounds such as butanol and aniline. In general it does not cause denaturation of the protein, which can be redissolved when the salt is removed. The most convenient method of separating proteins from salts is by *dialysis* in a tube of semipermeable membrane such as parchment, collodion, or (nonwaterproofed) cellophane. The ions of salts and the molecules of most relatively simple organic compounds readily pass through such membranes into the water placed outside; the large, colloidal, protein molecules are incapable of such diffusion.

Salting out by high concentrations of neutral salts must not be confused with precipitation by the salts of heavy metals, such as copper and mercury, referred to above. These latter need be used only in small amounts, are most effective on the alkaline side of the isoelectric point, and result in the formation of complex coordinated compounds. The use of raw egg white as an antidote for poisoning by bichloride of mercury is a practical application.

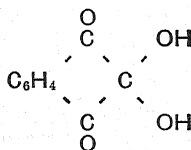
21-17 Color Reactions. Laboratory manuals of biochemistry describe many color tests for proteins. Most of these depend upon reactions due to groups contained in one or more of the constituent amino acids and are, in effect, tests for these particular acids. For example the yellow color produced by nitric acid on the hands (*xanthoproteic* reaction) is a result of nitration and shows that the skin proteins contain some readily nitrated aryl radical such as the hydroxyphenyl group of tyrosine. A positive result in any one test may be given by some simple, nonprotein substance, and a true protein may give no response if it happens to be deficient in a particular amino acid. But the presence or absence of protein can be shown conclusively by using several of the tests. Two color reactions more characteristic of the protein molecule as such are the biuret and ninhydrin tests.

Biuret Test. This is made by adding a very little cupric sulfate solution to the substance to be tested, dissolved or suspended in strong sodium hydroxide. A positive reaction is the appearance of a bluish violet, violet, or pink color. Proteins and all their products of hydrolysis down to tripeptides (and also the amino acids histidine and threonine) respond to

this test—the shade of color varying with the nature of the substance. The test gets its name from the fact that a strong reaction is given by *biuret*, a colorless compound readily formed by heating urea. The close resemblance between its structure and the groupings found in a typical peptide will be apparent on comparing their formulas.



Biuret

Ninhydrin
Triketohydrindene hydrate

Ninhydrin Test. The aromatic compound usually called ninhydrin gives an intense blue color with all the true α -amino acids (proline and hydroxyproline do not respond). This serves as an extremely delicate test for α -amino acids, in biological fluids for example, and also for proteins provided the latter contain at least one side chain in which a free carboxyl and an amino group are attached to the same carbon atom.

21.18 Proteins in Industry. The outstanding use of proteins is as *food* for man and beast (Chap. 27). Such higher organisms require for growth and health a supply of α -amino acids furnished by hydrolyzing food proteins in their digestive tracts. Cattle and hog raising, meat slaughtering and packing, poultry and egg production, fishing, and the manufacture of cheese are some of the major industries based on the need for proteins in human food. The aggregate dollar value of the products marketed by these food industries dwarfs all other commercial uses of proteins.

Yet some of the others are important. The textile fibers *wool* and *silk* are both proteins. *Leather* is manufactured by tanning the protein, collagen, of animal hides. *Gelatin* is produced by boiling with water clean rawhide trimmings and hooves; it is used in food products such as ice cream and marshmallows and in making the emulsions of silver halides on photographic film. *Glue*, which is similar in nature to gelatin but produced under less rigorous sanitary conditions, is used both as an adhesive and in sizing paper to impart a gloss finish. *Casein* is the chief protein of milk, of which it composes about 3 per cent. After separation from the skim milk of creameries, casein is used for such varied purposes as sizing leather, paper, and textiles, and in cold-water paints and waterproof adhesives. Artificial textile fibers have been manufactured in a limited way from casein and from the proteins of soybeans and peanuts; the most successful is Vicara, produced from the zein of corn.

Pure amino acids suitable for medicinal use and feeding experiments

are produced commercially, though on a small scale, by hydrolyzing suitable proteins and isolating individual compounds. Glutamic acid is exceptional in the quantity produced (10 million pounds of the monosodium salt, USA, 1951). The sodium salt has the property of imparting a meatlike flavor to vegetable foods and is used in cooking. It is manufactured from protein waste of beet-sugar refining.

21-19 The Nitrogen Cycle. Life requires proteins, and proteins require nitrogen. No animals and only a few plants are able to utilize the chemically inert free nitrogen of the atmosphere (clover, peas, and soybeans do so with the aid of nitrifying bacteria present in their root nodules). Most plants take up this essential element from its simple inorganic compounds—nitrates, nitrites, and ammonium salts. With the aid of water, carbon dioxide, solar energy, and enzymes they construct α -amino acids and combine these into plant proteins.

Man eats plant proteins and also those of flesh, fish, and fowl which have been derived from plant proteins. Under normal circumstances he excretes regularly, mainly as urea in the urine, an amount of nitrogen equal to that contained in the food consumed. At death all organic nitrogen is returned to the soil. Here, with the aid of bacteria and enzymes, urea and decaying proteins are converted into ammonium salts, nitrites, and nitrates. Thus the same atoms are once more in condition to serve as plant food and repeat this *nitrogen cycle*.

Need for Fertilizers. The nitrogen cycle is not quite quantitative. When proteins are burned, and to some extent when they decay, free nitrogen is formed and returned to the atmosphere. Furthermore, under modern conditions, the nitrogen removed from the soil of a particular tract, e.g., the pound of nitrogen contained in each bushel of wheat harvested on a Dakota farm, is seldom returned to that field. Thus arises the need for *nitrogenous fertilizers*, the production of which is one of the largest chemical industries. The fixation of atmospheric nitrogen holds first place—the production of ammonia by the Haber process and the manufacture of calcium cyanamide. Auxiliary sources are Chilean sodium nitrate and by-product ammonia from coking. Ammonia from any source is used principally as the sulfate or other salt, but large quantities are converted into fertilizer urea. Calcium cyanamide is ground and used directly on the soil.

Questions

1. (a) Give the essential structure of the natural amino acids, including their configuration. (b) Describe and illustrate the three different classes.
2. Write structural equations for all reactions involved in the synthesis of: (a) phenylalanine from $\text{C}_6\text{H}_5\text{CH}_2\text{CHBrCOOH}$ by two methods; (b) leucine from isovaleraldehyde, $(\text{CH}_3)_2\text{CHCH}_2\text{CHO}$.

3. Summarize the evidence for the existence of α -amino acids as dipolar ions.
4. Glycine and sodium hydroxide (0.1 formula weight of each) are dissolved in water. Trace what happens as 0.2 formula weight of HCl is slowly stirred in.
5. Explain clearly the meaning of the term "isoelectric point" and explain why it usually does not lie at pH 7.
6. Write structural equations for the reactions, if any, which are to be expected when alanine is treated with cold solutions of: (a) HCl; (b) NaOH; (c) $\text{HNO}_2 + \text{HCl}$; (d) $\text{C}_6\text{H}_5\text{COCl} + \text{NaOH}$; (e) $\text{C}_4\text{H}_9\text{OH} + \text{HCl}$.
7. How does the simplest amino acid, glycine, differ in structure from all the others? What difference in a physical property results?
8. When proteins are hydrolyzed by alkalies, the amino acids are usually racemized and obtained as DL mixtures. Can you suggest a mechanism for this racemization by alkalies? (Cf. Sec. 17-10.)
9. (a) Give the origin of the term "protein" and explain accurately why this name is justified. (b) Would you say that the fundamental need of the animal body is for nitrogen? For proteins? For what? Explain fully.
10. If a protein containing 16 per cent nitrogen has a molecular weight of 70,000, how many nitrogen atoms are present in each molecule?
11. Analysis of oxyhemoglobin obtained from horse blood shows that it contains 0.335 per cent of iron and 0.39 per cent of sulfur. (a) What is the ratio between the number of S atoms and Fe atoms contained in each molecule? (b) Assuming that the molecule contains four atoms of iron, what is the minimum molecular weight?
12. Explain why, apart from any experimental errors, the percentages of the different amino acids isolated from a protein (Table 21-2) should total more than 100 per cent.
13. Justify, from a scientific standpoint, St. Paul's statement: "All flesh is not the same flesh; but there is one kind of flesh of men, another flesh of beasts, another of fishes, and another of birds." (1 Cor. 15:39.)
14. Starting with α -amino acids and using the carbobenzoxy method, show all the reactions necessary in forming a tripeptide.
15. Using one molecule each of four different α -amino acids, how many different tetrapeptides are possible?
16. If a protein yields a large amount of nitrogen in a Van Slyke determination before hydrolysis, what type of amino acid must it contain in considerable amount?
17. Fibroin, the protein of worm silk, contains about 70 per cent of glycine and alanine. Disregarding its other amino acids, show how the structure of silk resembles and differs from that of nylon.
18. A certain protein gives a black precipitate when its solution is heated with sodium hydroxide and lead acetate. Which amino acids (Table 21-1) could be responsible for this reaction?
19. Name the products of protein hydrolysis in the order of decreasing complexity and write a type equation for the reactions through which they are produced.
20. (a) Explain the basis of the division of the proteins into the three main classes recognized by physiologists and biochemists; (b) What are nucleoproteins? Nucleotides?
21. Describe the structure of a protein at its isoelectric point and summarize the physical properties characteristic of isoelectric protein.
22. Explain: (a) why acidity progressively decreases when ground lean beef is digested in an incubator by a solution containing pepsin and hydrochloric acid (initially 0.1N); (b) why gelatin combines with ferrocyanide ion, from $\text{K}_4\text{Fe}(\text{CN})_6$, only on the acid side of its isoelectric point.

23. Explain how the proteins of the blood can aid in preventing changes in hydrogen-ion concentration when acid or alkali is added.
24. (a) Discuss the exact significance of protein color tests. (b) In what way does the biuret reaction differ from most other color tests?
25. Trace the history of a molecule of atmospheric nitrogen through its fixation by the Haber process, application to the soil as fertilizer, incorporation into a plant protein and the use of the latter as animal food, to its reappearance in the soil as ammonium salt.

CHAPTER 22

POLYFUNCTIONAL AROMATIC COMPOUNDS

I. SOME GENERAL PRINCIPLES

Many derivatives of aromatic hydrocarbons have been isolated from plants and animal bodies, but not many occur here in useful quantities. The aromatic compounds which are important in chemical industry and in everyday life are, nearly all, factory products. The raw materials for their production are *benzene*, *toluene*, *naphthalene*, and a few other compounds obtained as by-products of coking (Sec. 6.26) or produced from petroleum (Sec. 6.18). These are converted through chemical reactions into many intermediates and, finally, into the finished products consumed by the general public (Sec. 23.1). Tracing some of these chemical transformations is a useful way to study the polysubstituted and mixed aromatic compounds and to grasp the relations among them. After discussion of some general principles here, this is done in Chapters 23 and 24.

22.1 General Synthetic Reactions. The manufacture of intermediates and finished products from the parent aromatic hydrocarbons is an outstanding example of the usefulness of *general* synthetic methods. Starting with benzene, toluene, and naphthalene, hundreds of different products are produced through the appropriate use of some 10 or 12 reactions.

The first step is nearly always a typical aromatic substitution—*chlorination*, *nitration*, *sulfonation*, or a *Friedel-Crafts reaction*. Next in frequency come *alkali fusion* (replacement of SO_2OH by OH) and *reduction*—usually of NO_2 to NH_2 . A second group of reactions which are important, though used less often than the first, includes *amination* (replacements of Cl , etc., by NH_2), *oxidation* (e.g., of side chains to COOH), *alkylation* of amines and phenols, *hydrolysis*, *diazotization*, and *coupling*.

Practical Methods. In order to qualify for industrial production, a substance must have *useful properties* which create a demand for it; also it must be producible at a cost consistent with this demand. Production costs involve many factors such as the price of raw materials, the number of operations involved, and the time and labor required for separations and purifications. In a chemistry course we are concerned primarily with the fact that over-all cost depends in large measure on the *yields* obtainable.

This practical objective of *low costs through good yields* is intimately related to the theoretical principles which explain directing influences in substitution, activation and deactivation, and other mutual influences.

22.2 Utilization of Directing Influences. The industrially important aromatic compounds synthesized from benzene, toluene, and naphthalene are those which can be obtained in good yields by taking advantage of *favorable* directing influences. Thus the favored *o*- and *p*-dichlorobenzenes are produced in millions of pounds, for sale at around 15 cents a pound, by direct chlorination of benzene; their *meta* isomer is a research chemical, made by an expensive indirect method, and sold at \$7 per hundred grams.

The practical chemist never attempts to *oppose* directing influences; instead he seeks means to utilize them. This is often possible by considering different sequences in which the same reactions may be used. For example, one can obtain a good yield of either *para*- or *meta*-aminobenzenesulfonic acid through the two sequences indicated in Figure 22-1.

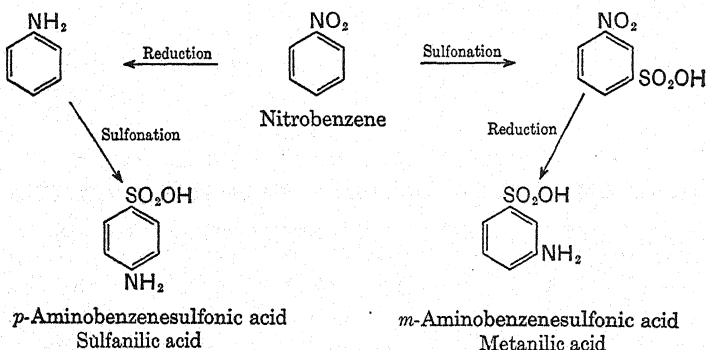
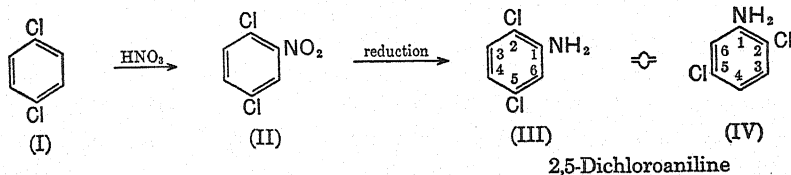


FIG. 22-1 The same two reactions, used in reversed order, give good yields of *para* and *meta* disubstitution products of benzene.

The reactions used—sulfonation and reduction—are identical. But, on account of the difference in the directing influences of the nitro and amino groups, sulfonation followed by reduction yields almost exclusively the *meta* compound while reduction followed by sulfonation gives the *para* (with some of the *ortho*) isomer. Figure 22-2 shows a similar example.

The manufacture of 2,5-dichloroaniline, (IV) below, illustrates the importance of starting with the right material. Naturally, one thinks of using aniline; but if aniline were dichlorinated, the strongly *ortho*- and *para*-directing amino group would send the chlorine atoms to the 2,4 or 2,6 positions. If we think of chlorinating nitrobenzene, with the intention of later reducing NO₂ to NH₂, we realize that the *meta*-directing nitro group would lead to 3,5-dichlorination. Both these methods are there-

fore discarded. The key to the problem lies in noting that the chlorine atoms in the desired product are *para* to each other, which suggests starting with the readily obtainable *p*-dichlorobenzene (I). On mononitration this gives (II) as the only possible product, and simple reduction yields (III), the desired end product.



The "trick" here is to recognize that (III) and (IV) are identical and represent the same compound.

Limitations. In planning any sequence of reactions it is important to consider the probable effects of any treatment on *all* groups in the molecule. For example, alkali fusion for replacement of SO_2OH by OH is feasible if the other groups present are stable under that rather drastic

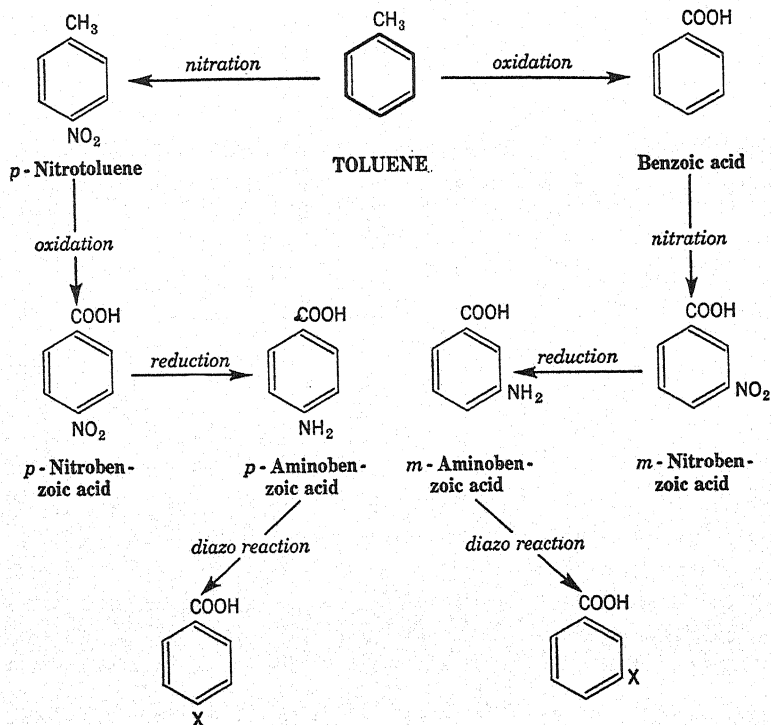
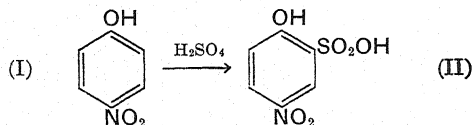


FIG. 22-2 Many *para*- and *meta*-substituted benzoic acids are made from toluene by using the same reactions in different sequences.

treatment. But if the molecule contains halogen, this also is apt to be replaced by OH; if it contains COOH, decarboxylation may be expected. Another important limitation is the sensitiveness of phenols and primary aryl amines to oxidizing agents. These compounds may not be subjected to the action of strong oxidants unless the sensitive groups are suitably protected. It will be noted that, in both sequences of Figure 22.2, the methyl group is oxidized before the amino group is introduced.

22.3 Reinforcing and Opposing Influences. It is sometimes but not always possible to predict the direction of further substitution on a benzene derivative with two substituents. This will depend on the nature of these substituents and upon their relative positions.

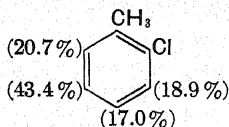
With two identical groups *para* to each other, only one product is possible when a third enters. The result is also predictable with two unlike groups in the *para* positions if their directing influences *reinforce* each other, as they do in *p*-nitrophenol (I). Position 2 (or 6) is *ortho* to the *o*-and-*p*-directing OH group and *meta* to the *m*-directing NO₂ group; the compound actually gives a 100 per cent yield of the 2-sulfonic acid (II):



Even when directing influences oppose each other, it is possible to get good yields of a single product if one is much more powerful than the other; this was illustrated for *p*-cresol in Section 5.19. In *p*-chlorotoluene, however, with two *o*-and-*p* substituents of about equal strength *opposing* each other, the product of mononitration is a mixture of (III) and (IV):



Other situations present possibilities which are still less predictable. It will suffice to illustrate by the nitration of *o*-chlorotoluene. Each of the four positions open is *ortho* or *para* to one of the *o*-and-*p*-directing groups. The actual product of mononitration is a mixture of the four possible isomers in the proportions indicated below:



ORIGIN OF DIRECTING AND ACTIVATING INFLUENCES

22.4 The principal *facts* concerning directing influences in aromatic substitutions were summarized in Sections 5-18 and 5-19. Their practical consequences have been pointed out in various places and, particularly, in the sections just above. It remains to explain these facts in terms of the theory which seems most useful at the present time. Before giving details, this may be summarized as follows:

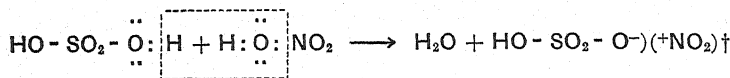
1. Substitution of hydrogen on an aromatic nucleus is nearly always the result of attack by an *electrophilic* reagent. The latter furnishes an electron-deficient, positive group which unites with one of the ring carbons by appropriating a pair of its electrons. The hydrogen atom on this carbon is displaced and leaves the organic molecule in combination with an electronegative fragment of the reagent.

2. Substitution by an electrophilic reagent is most likely to occur on that ring carbon which offers the most readily available pair of electrons. The availability of an electron pair is influenced mainly by whatever groups or atoms, other than hydrogen, are already attached to the ring. If, in the benzene derivative $C_6H_5.X$, the nature of X^1 is such that it can throw electrons *into* the ring, the *ortho* and *para* carbon atoms acquire $-\delta$ charges which render them more susceptible to substitution by electrophilic reagents. If the nature of X is such that it attracts electrons *away* from the ring, substitution in all positions is more difficult than in benzene, but least difficult in the *meta* positions. Therefore, *meta*-directing substituents are deactivating while *ortho*- and *para*-directing substituents (except halogen atoms, Sec. 22-9) are activating.

22.5 Electrophilic Reagents. The common reagents that displace nuclear hydrogen atoms are nitric acid, sulfuric acid, chlorine and bromine in the presence of iron, and alkyl and acid halides in the presence of $AlCl_3$ and similar catalysts. All these are strongly electrophilic reagents, acting by virtue of an electropositive fragment, as follows:

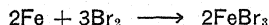
Nitration and Sulfonation. Practical nitrations of aromatic compounds are always conducted with mixtures of concentrated HNO_3 and H_2SO_4 . It has been shown quite definitely that the effective agent is the nitronium ion, NO_2^+ , which is deficient by one electron and therefore carries a unit positive charge. This does not mean that these ions necessarily exist free in the reagent; they may be present in active complexes which yield them at the moment of reaction, *e.g.*,

¹ The symbol X is used in the discussions of this chapter to represent *any atom or group other than hydrogen*. Halogen atoms are designated by their specific symbols, Cl , Br , etc.

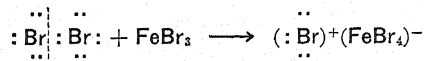


It is highly probable also that sulfuric acid acts as a sulfonating agent through the positive ion, $^+\text{SO}_2\text{OH}$, though the evidence here is less conclusive than for nitric acid.

Halogenation. The function of the catalyst, usually metallic iron, is to furnish electron-deficient Cl^+ or Br^+ ions. The initial reaction, of the type

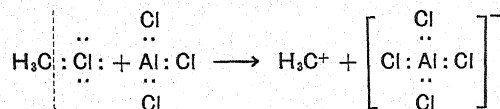


is well known. Under the practical conditions of halogenation (excess of free halogen and the absence of water) this is followed by the further reaction

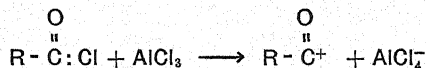


The strongly electrophilic Br^+ or Cl^+ ion is the agent which attacks the aromatic nucleus.

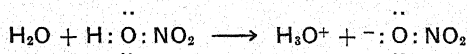
Friedel-Crafts Reaction. Alkyl halides are nonconductors of electricity, but they dissolve anhydrous aluminum chloride to form conducting solutions with *aluminum in the anion*:



That is, strongly electrophilic *carbonium ions* are formed. The formation of carbonium ions is likewise the function of AlCl_3 when it serves as a catalyst in the alkylation of aromatic hydrocarbons with alkenes (cf. Sec. 23-4) and in the ketone synthesis (Sec. 10-18), where it reacts with the acid halide as follows:



† The student may be shocked at the suggestion that nitric acid acts in this way when he has become accustomed to its very different behavior in water solutions:

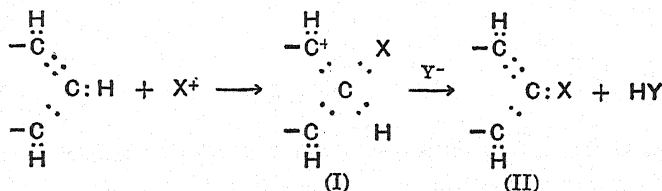


He must remember that the mixed acids used in nitrations contain more H_2SO_4 than HNO_3 and *very little water*.

In some reactions it is possible to replace AlCl_3 by another catalyst which is capable of forming carbonium ions, *e.g.*, BF_3 or anhydrous HF .

The halides AlCl_3 and BF_3 (and others of similar structure) are sometimes called "Lewis acids." The Group III metallic atom in each of them has only a sextet of electrons and readily accepts two more, to complete its octet, by adding some ion or molecule which carries an unshared pair (formation of a coordinate covalence, Sec. 1-9). The ability to accept an electron pair in this manner, as in the formation of the hydronium ion, is the most distinguishing property of the proton, H^+ . Hence, G. N. Lewis included AlCl_3 and BF_3 within his definition of acids.

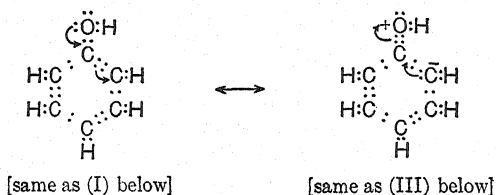
22-6 Aromatic Substitution. Summarizing the preceding section, the reagents commonly used to substitute hydrogen on an aromatic nucleus are compounds of the general type XY which, before or at the moment of reaction, are capable of yielding the ions X^+ and Y^- . The driving force in substitution is the tendency of the electron-deficient ion, X^+ , to combine with a pair on a nuclear carbon atom. This may be pictured with reasonable similitude as follows (showing only three atoms of the aromatic ring):



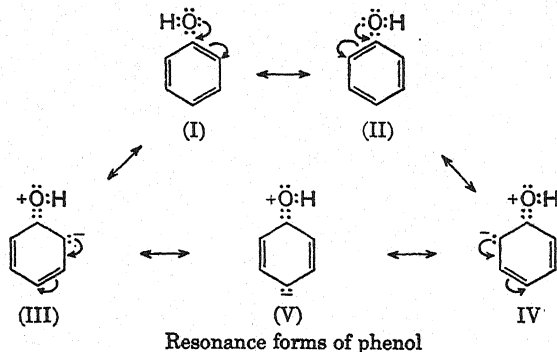
Probably there exists momentarily the complex (I) in which both X and H are joined to the carbon atom which is attacked. The presence of Y^- is doubtless helpful in removing the proton, but the great "drive" toward (II) is the restoration of ring resonance.

This conception of the substitution reaction implies that the electrophilic reagent X^+ ($^+\text{NO}_2$, $^+\text{SO}_2\text{OH}$, Cl^+ , R^+ , etc.) will attack the nuclear carbon which has a pair of electrons most readily available. The role of other groups attached to the nucleus in making electrons readily available in some positions, and scarce in others, is explained as follows.

22-7 *Ortho*-and-*para*-directing Groups. The hydroxyl group in phenol is 100 per cent *ortho*-and-*para*-directing when this compound is chlorinated, brominated, or nitrated (Table 5-2). We have also encountered much evidence (*e.g.*, Sec. 8-29) that the OH group strongly *activates* the 2, 4, and 6 positions. These facts are explained in terms of the various extreme forms which contribute to the hybrid structure of the phenol molecule. Two Kekulé forms, (I) and (II), can be written as for every benzene derivative. Additional extreme forms arise from electronic displacements in the directions indicated by the curved arrows:



Passing to the less cumbersome conventional formulas, the possibilities¹ may be indicated as follows:



In summary: Resonance in the phenol molecule increases electron density on the *ortho* and *para* carbon atoms, which are thus made more susceptible to electrophilic substitutions.

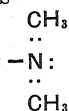
It is most important to recognize that the center of electron density in the phenol molecule is actually very close to that implied by the Kekulé formulas, (I) and (II). Resonance shifts the electron cloud slightly *in the directions* indicated in the other formulas—not *to* these positions. Any displacement toward the ring sets up a corresponding positive charge on oxygen, and this *separation of charges* acts to restrain further movement in the direction which gave rise to it. Consequently, forms (III), (IV), (V) make only minor contributions to the actual state of the hybrid molecule.

Other *ortho*-and-*para*-directing groups and atoms (Sec. 5-19) act like the OH group toward increasing electron density on C², C⁴, and C⁶. With the exception of halogen atoms (Sec. 22-9) they all activate these

¹ In order to avoid undue complication of the formulas, reverse arrows representing restoration of the Kekulé forms have been omitted.

It is *not* possible for a charge to rest on the *meta* positions, C³ and C⁵. Referring to the fully expanded formula above, with the charge on C², it may be seen that if an electron pair moves from C² to C³, the latter has *five* pairs. Since this is impossible, the extra pair must be relayed on to C⁴ or else returned to C².

positions, though in varying degrees. The most powerfully activating groups

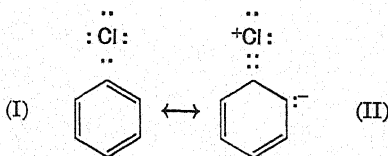


The attraction on the ring electrons exerted by the $+\delta$ nitrogen atom distorts the Kekulé forms (I and II) toward the other three extreme forms. These make only minor contributions to the hybrid structure because the electron shifts which would produce them involve the separation of charges (compare phenol, above). But the effect of the resonance in which they are involved is to *decrease electron density throughout the ring* and, particularly, on C², C⁴, and C⁶. Thus, all positions are deactivated toward electrophilic substitutions and, more especially, the *ortho* and *para* positions. If and when such a substitution does occur, it is most probable at a *meta* position.

Reviewing the list of common groups¹ which are prevailingly *meta*-directing and deactivating (Sec. 5-19), it may now be seen that the key atom in each of them is either the donor to a coordinate bond or is joined by a double bond to a more electronegative atom. Thus the key atom carries some $+\delta$ charge, the magnitude of which varies from group to group. To the extent that this charge is able to withdraw ring electrons, all positions are deactivated, but this effect is least in the *meta* positions.

22.9 The Halogen Anomaly. Halogen atoms attached to the benzene ring are *ortho*- and *para*-directing, as indicated by the data for chlorobenzene in Table 5-2. But hydrogen atoms in chlorobenzene and other aryl halides are less easily substituted than in benzene, showing a deactivating effect of the halogen atom. This anomalous situation is the resultant of opposing tendencies.

One tendency arises in resonance with the ring. Acting as in vinyl chloride (cf. Sec. 15-5), the chlorine atom may use one of its unshared electron pairs in the direction of forming a double bond with carbon, as in (II). The measured shortening of the chlorine-carbon bond (1.70 Å vs. the normal 1.76 Å) indicates an actual shift in this direction. The effect is to place a $-\delta$ charge on C², C⁴, and C⁶ as in phenol [formulas (III), (IV), (V) of Sec. 22-7], which explains why the chlorine atom is *ortho*- and *para*-directing.



The *opposing tendency* is due to the inductive action of the electronegative chlorine atom (Sec. 1-9). This power of the chlorine atom to draw

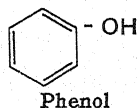
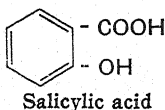
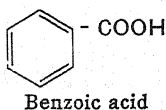
¹ The most powerful *meta*-directing group, $(\text{H}_3\text{C})_3\text{N}^+$, was not listed because it is rarely encountered. This group carries a *unit* charge as in any quaternary ammonium ion.

electrons toward itself has been noted in various connections, notably in the strength of the chlorine-substituted acetic acids (Table 20·1). In chlorobenzene, induction must result in the *withdrawal* of ring electrons—that is, in a shift which directly opposes¹ the resonance effect. Judging from the fact that substitution at any position in chlorobenzene is more difficult than in benzene, it must be concluded that the inductive effect predominates. Yet, because of the resonance effect, deactivation is least in the *ortho* and *para* positions.

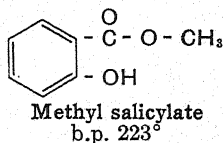
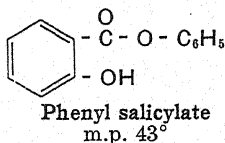
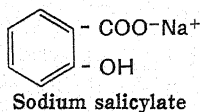
RELATIONS BETWEEN PROPERTIES AND STRUCTURE

22·10 Prediction of Properties. The rule of the independent action of functional groups (Sec. 15·1) is invaluable in predicting the properties of polysubstituted and mixed aromatic compounds. This is well illustrated by salicylic acid and some of its derivatives.

Salicylic acid (*o*-hydroxybenzoic acid) forms colorless crystals (m.p. 159°C) which, like those of benzoic acid, dissolve freely in alcohol and ether but are only sparingly soluble in water. Its chemical properties are derived in part from benzoic acid and in part from phenol, to both of which it is structurally related:



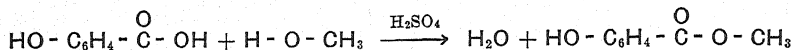
Like benzoic acid, it dissolves in solutions of sodium hydroxide and *also* in sodium bicarbonate and yields the carboxylate salt, sodium salicylate. By the other usual reactions of the COOH group it likewise yields an acid chloride, an amide, and many esters of the type of phenyl salicylate (the drug, *salol*) and methyl salicylate:



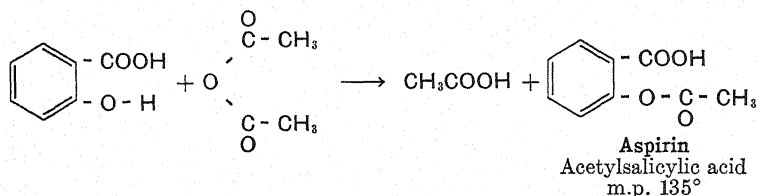
The latter is manufactured by heating salicylic acid with methanol and a

¹ Physical evidence of such an opposition is found in the lower dipole moment of chlorobenzene vapor (1.72 D) as compared with alkyl chlorides (1.87 D for CH₃Cl and 2.05 D for C₂H₅Cl). The dipole moments of nitrobenzene (4.24) and *p*-nitrochlorobenzene (2.6 D) are also significant. The difference of 1.64 D is almost exactly the moment of chlorobenzene. Obviously, the two groups must be operating *against* each other in the molecule of *p*-nitrochlorobenzene, each tending to *withdraw* electrons from the ring.

little sulfuric or hydrochloric acid, the standard method for esterifying carboxylic acids:



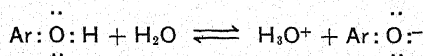
Like *phenol*, water solutions of salicylic acid give a deep-purple coloration with ferric chloride and a precipitate with bromine water. The nuclear hydrogen atom *para* to the hydroxyl group is readily replaced by nitration and by sulfonation. Acid chlorides and anhydrides acylate the *phenolic* hydroxyl group to give esters of the type of aspirin, which is manufactured by heating salicylic acid with acetic anhydride:



The chemical properties of methyl salicylate and aspirin likewise show the differences that would be predicted. Methyl salicylate, which retains the phenolic hydroxyl group, gives the expected color reaction with ferric chloride and a precipitate with bromine water; it dissolves like phenol in solutions of sodium hydroxide but, lacking a carboxyl group, differs from salicylic acid in failing to dissolve in sodium bicarbonate. Aspirin, in which the phenolic hydroxyl has been altered, gives no reaction with ferric chloride¹ or bromine water; but, because the carboxyl group remains unaltered, it is strong enough as an acid to dissolve readily in sodium bicarbonate.

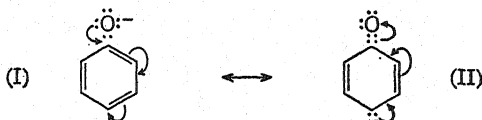
Unpredictable Properties. It is to be expected, of course, that important exceptions to the rule of independent action will be encountered among the aromatic mixed compounds as they were in the aliphatics. The origin of *some* of these exceptions can be clarified by applying the principles explained above (Secs. 22·7 to 22·9). The following are illustrative.

22·11 Acidity of Phenols. The extent to which a phenol is ionized depends on the position of equilibrium in the system:



¹ A faint reaction in this extremely delicate test may come from minute traces of salicylic acid present as an impurity or formed by hydrolysis when a solution of aspirin stands.

The loss of a proton—reaction toward the right—is made easier than in an alcohol by the small $+\delta$ charge on the oxygen atom which arises from resonance in the phenol molecule (Sec. 22·7). Recombination of ions—reaction toward the left—is retarded because the phenoxide ion is stabilized by resonance somewhat more highly than the molecule. Besides the two Kekulé forms represented by (I), in which the negative charge is on oxygen, there are three extreme forms analogous to (II), in which this charge is on an *ortho* or the *para* carbon atom:



Two resonance forms of the phenoxide ion

The migration of electrons in the phenoxide ion indicated in the formation of (II) from (I) does *not* involve any separation of charge as in the corresponding forms of the phenol molecule [(III), (IV), (V), of Sec. 22·7]. Such forms therefore make somewhat more important contributions¹ to the actual state of the ion, which is stabilized accordingly and its formation promoted. It must be remembered, however, that phenol is a very *weak* acid ($K_a = 1.3 \times 10^{-10}$). This is true likewise of the cresols, naphthols, and all other phenols except those substituted by NO_2 or other electronegative groups.

TABLE 22·1 IONIZATION CONSTANTS OF SOME NITROPHENOLS

Phenol (hydroxybenzene).....	1.3×10^{-10}
<i>p</i> -Nitrophenol.....	6.9×10^{-8}
<i>o</i> -Nitrophenol.....	6.2×10^{-8}
3,5-Dinitrophenol.....	2×10^{-7}
2,4-Dinitrophenol.....	1×10^{-4}
2,6-Dinitrophenol.....	2.7×10^{-4}
2,4,6-Trinitrophenol† (picric acid).	4.2×10^{-1}

† Picric acid is too strong for its true ionization constant to be measured in water solutions. This approximate value serves to compare it with the other compounds in the table.

Nitrophenols. The acidity of phenols is increased greatly by nitro groups *ortho* or *para* to the hydroxyl. Thus, 2,4- and 2,6-dinitrophenol are stronger acids than acetic, for which reason they dissolve in sodium bicarbonate solutions as well as in sodium hydroxide. Picric acid, 2,4,6-trinitrophenol, is a stronger acid than oxalic and comparable in strength to trichloroacetic acid (Table 20·1).

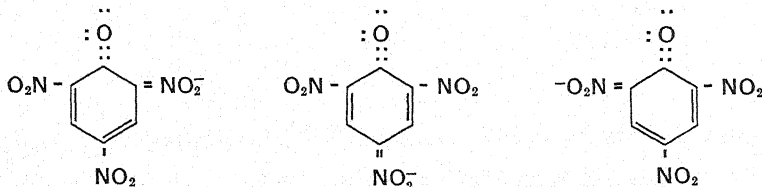
¹ If the interested student will compare the relative positions of oxygen and carbon in the electronegativity scale (Sec. 1·9) he should be able to see why (II) and its analogous forms do not make *major* contributions to the hybrid phenoxide ion.

This effect of *o*- and *p*-nitro groups may be explained as follows, taking *p*-nitrophenol as an example. Resonance in the *p*-nitrophenoxide ion is between extreme forms typified by (III) and (IV):



Two resonance forms of the *p*-nitrophenoxide ion

The electron-attracting NO_2 group facilitates electronic shifts toward (IV). Consequently, (IV) makes a more important contribution to the structure of the *p*-nitrophenoxide ion than does (II) to that of the phenoxide ion. Because of this increase in resonance, *p*-nitrophenol is more highly ionized. (The relation to the color of *p*-nitrophenol solutions is discussed in Section 25-25.) Picric acid has three reinforcing nitro groups, and the picrate ion receives major contributions from each of the equivalent forms:



22-12 Basicity of Aryl Amines. The unshared electron pair of the nitrogen atom in an aryl amine is involved in resonance with the ring in the sense indicated by



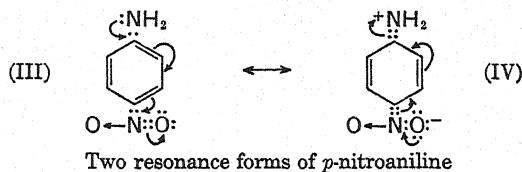
Two resonance forms of aniline

As with phenol, we may write two other extreme forms with the negative charge on C^2 and C^6 , respectively. The groups NH_2 , NHCH_3 , and $\text{N}(\text{CH}_3)_2$ highly activate the *ortho* and *para* positions toward electrophilic substitutions, thus indicating that forms like (II) make fairly important contributions to the hybrid molecule.

The strength as a base of *any* amine depends on the availability, for proton binding, of the unshared electron pair on the nitrogen atom. To the extent that these electrons of an aryl amine are involved in resonance with the ring, they are not available for proton binding. This explains

why aniline ($K_b = 4.6 \times 10^{-10}$) and other true aryl amines are much weaker bases than ammonia and the alkyl amines. Benzyl amine, $C_6H_5.CH_2.NH_2$, in which resonance with the ring is substantially eliminated by the insulating CH_2 group, is a base ($K_b = 2 \times 10^{-5}$) of about equal strength with ammonia.

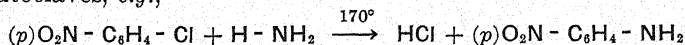
Effect of Nitro Groups. The low basicity of aryl amines is still further reduced by nitro groups in the *ortho* and *para* positions. For example, the constant for *o*-nitroaniline is close to 1×10^{-14} and that for *p*-nitroaniline is 1.2×10^{-12} . Resonance in the latter is between forms represented by



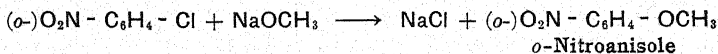
The nitro group operates as in the nitrophenols to withdraw electrons from the ring; this promotes the entry of the N electrons into resonance with the ring and makes them still less available for proton binding.

The relatively high contribution of (IV) to the molecule of *p*-nitroaniline is further indicated by a comparison of dipole moments. These are 4.21 D for $C_6H_5.NO_2$ and 1.48 D for $C_6H_5.NH_2$. The corresponding value for *p*-nitroaniline is 6.1 D. This shows that, as assumed above, the NH_2 and NO_2 groups act cooperatively. The excess of 6.1 over the sum of 4.21 and 1.48 shows further that *each augments the other* in shifting the actual state of the molecule in the direction of (IV). This high degree of resonance in *p*-nitroaniline also has a direct relationship to its yellow color (Sec. 25·4).

22·13 Reactivity of Aryl Halides. The well-known difficulty in replacing the halogen atom of chlorobenzene and similar aryl halides can be overcome by introducing nitro groups into the *ortho* and *para* positions. Thus, in sharp contrast to the parent chlorobenzene, 1-chloro-2,4-dinitrobenzene exchanges its halogen atom for hydroxyl when boiled in an open vessel with as mild an alkali as sodium carbonate solution. With even one nitro group present, the chlorine atom may be replaced by NH_2 on heating with ammonia under pressures readily obtained in ordinary factory autoclaves, *e.g.*,

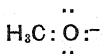


In like manner, *o*-chloronitrobenzene enters readily into the Williamson synthesis:



An extreme example is *picryl chloride*, 2,4,6-trinitrochlorobenzene, which has three activating nitro groups. Picryl chloride reacts about as readily as an aromatic *acid* halide such as benzoyl chloride; for example, cold aqueous ammonia replaces the chlorine atom by NH_2 to form picramide (2,4,6-trinitroaniline).

This activation of halogen by nitro groups is explained as follows. The reagents which displace halogen atoms, such as

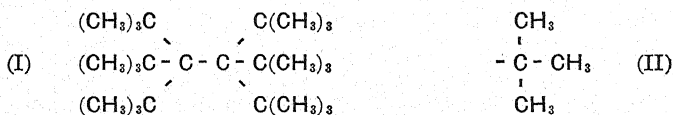


are all *nucleophilic*. They are repelled by electrons and can best displace a halogen atom when the latter is attached to a carbon with a relatively high $+\delta$ charge. Electron-attracting nitro groups in the 2,4, or 6 positions create a $+\delta$ charge on C^1 , which is therefore attacked readily with displacement of Cl^- .

SPACE EFFECTS

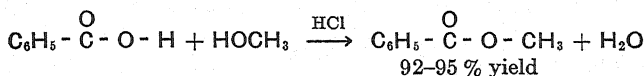
22.14 Steric Hindrance. Electronic mechanisms explain many facts in organic chemistry which, previously, could neither be predicted nor understood. But they do not explain why certain other reactions, reasonably to be expected, either fail to occur or are abnormally slow. Some of these can be understood in terms of *space* relations described under the general term *steric hindrance* or the *proximity effect*.

The theory of steric hindrance has a mechanical, rather than a chemical or electrical, basis. It starts with the reasonable assumption that two atoms, or two groups of atoms, cannot occupy the same space at the same time, any more than two people. From this it may be argued, for example, that a compound such as (I) is unlikely to exist because there is not enough room to pack six bulky radicals like (II) about the central carbon atoms.

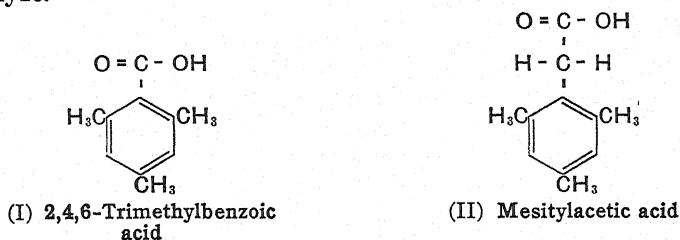


The theory leads to the conclusion that some reactions, otherwise to be expected, fail to occur because a reactive center is shielded, physically, by neighboring groups so that another substance is unable to approach closely enough to react. Some examples follow.

22.15 The standard method for preparing alkyl esters of aromatic acids is to dissolve the acid in an excess of the alcohol and pass dry hydrogen chloride into the hot solution. Reaction proceeds readily, and yields of 90 to 95 per cent of methyl esters are obtained with benzoic and many other aromatic acids:

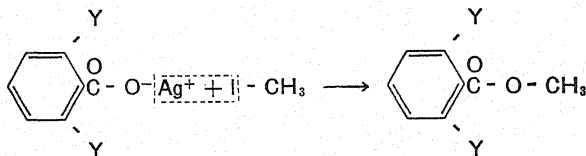


In sharp contrast, this treatment yields *no* ester with acids like (I) in which *both ortho positions* are substituted. Further, when the esters of these *o*-substituted acids are prepared by an indirect method (through their silver salts, as described below), they are abnormally hard to hydrolyze.



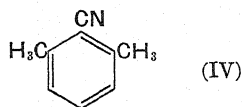
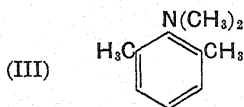
These retarding effects on esterification and hydrolysis are observed only when substituents are in the *ortho* positions; both reactions proceed normally with acids containing the same substituents *meta* or *para*. They cannot be explained in terms of any difference in the chemical nature or polarities of the substituents, for methyl groups, nitro groups, and bromine atoms are equally effective. Thus we are led to the physical explanation of steric hindrance—a shielding from reaction by the *bulk* of close-by *ortho* substituents. This is supported by the additional fact that *ortho* substitution no longer interferes when the carboxyl group is a little removed from the nucleus. For example, mesitylacetic acid (II) is esterified as readily as benzoic acid and its esters are hydrolyzed normally.

Another pertinent fact is that such “hindered” acids yield esters readily when their silver salts are treated with methyl iodide:



Probably this method succeeds because the reagent does not have to penetrate into the carboxyl group to remove the silver ion. In direct esterification, deeper penetration is necessary in order to break the carbon-oxygen bond (Sec. 12-6). The different results of the two methods afford a further illustration of the general rule that, if two apparently similar reactions proceed by different mechanisms, they are not comparable and a prediction based on one is apt to be wrong for the other.

22-16 There are many other reactions which are influenced powerfully by the presence of neighboring groups which appear to take no part in the actual chemical changes. It may be mentioned, for example, that the tertiary amine (III) gives no quaternary ammonium salt and that the nitrile (IV) is hydrolyzed with extreme difficulty.



Steric effects are doubtless involved also in aromatic substitutions. If the molecule contains an *ortho*-and-*para*-directing group, substitution in the *ortho* and *para* positions always proceeds simultaneously, but nearly always the *para* compound is formed in larger amount. The nitration of acetanilide, for example, gives 95 per cent *p*-nitroacetanilide, and only 5 per cent *ortho*. This is an extreme case, and a fairer general average is 60 to 70 per cent *para* and 40 to 30 per cent *ortho*. There is no reason to assign any higher polarity to the *para* carbon, and there are two *ortho* positions for one *para* (cf. footnote, page 84); so any excess of the *para* product is surprising. The theory of steric hindrance suggests that the *para* position is less shielded and is, therefore, more available for effective contacts with the reagent. Probably this is indeed an important factor. But it does not explain everything; for example, *alpha* substitution is the regular rule in the naphthalene series, although the *beta* positions are certainly less shielded.

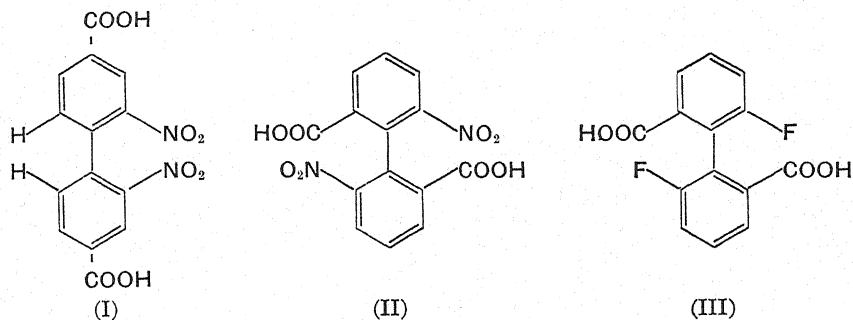
Abnormalities connected with groups in the *ortho* positions are so common that some authors use the term "ortho effect" almost synonymously with steric hindrance. But similar effects are observed also among open-chain compounds. The rates of esterification of aliphatic acids and alcohols and the hydrolysis of their esters are powerfully influenced by the accumulation of alkyl radicals near the reactive centers. *tert*-Butyl alcohol, $(\text{CH}_3)_3\text{C.OH}$, is esterified by carboxylic acids¹ much more slowly than any of its isomers; similarly, trimethylacetic acid, $(\text{CH}_3)_3\text{C.COOH}$, is esterified extremely slowly. These facts are only partially explained by the weak electron-releasing effects of methyl groups.

22-17 Optically Active Biphenyls. One direct and interesting consequence of steric hindrance is found in the asymmetry—and consequent optical activity—of certain molecules which do not contain an asymmetric carbon atom. This has been studied extensively among the substituted biphenyls.

The hydrocarbon biphenyl, $\text{C}_6\text{H}_5.\text{C}_6\text{H}_5$ (Sec. 23-3), is optically inactive,

¹ *Tert*-butyl alcohol is esterified by *halogen* acids far more readily than its isomers (Sec. 8-9).

and so are many of its derivatives, such as (I). But some others like (II) have been resolved (Sec. 17·8) into optically active components. All these contain *ortho* substituents bulky enough to keep the two rings from revolving about the single bond which joins them.



This interference in space of overlapping *ortho* groups holds one ring permanently in a plane which is, roughly, perpendicular to the plane of the other. If both rings are unsymmetrical,¹ the molecule will have one or the other of the unsymmetrical configurations indicated in Figure 22·3.

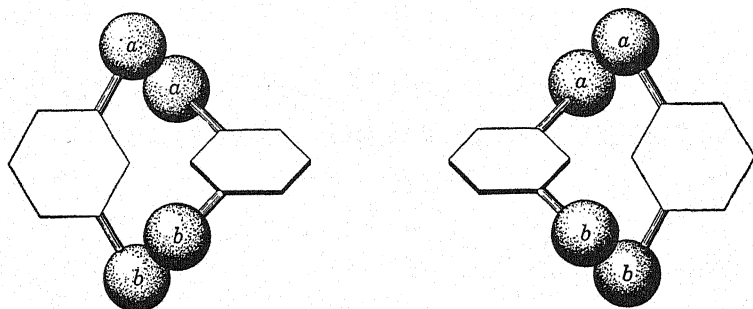


FIG. 22·3 Mirror-image forms of *ortho*-substituted biphenyls. Assume that the regular hexagon lies in the plane of the paper and the other is turned upward in the direction of making a 90° angle (the shaded edges being toward the observer).

These figures cannot be superimposed and represent mirror-image, dextro- and levorotatory isomers.

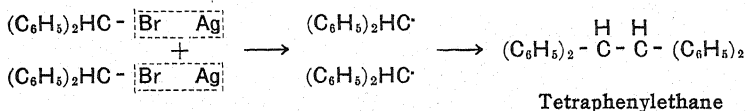
The optically active forms of (II) do not racemize easily, indicating much interference between the COOH and NO₂ groups (an overlap of 0.58 Å is calculated from known atomic radii). Compound (III) can be resolved, but is easily racemized. This indicates that, as would be expected, not much energy is needed to enable the COOH group to slip

¹ The requirement is that the ring may not have any plane of symmetry except the one which contains its six carbon atoms.

past the small fluorine atom. With the much larger iodine atom, even a hydrogen atom on the other nucleus interferes with revolution; a compound with the structure of (I), except that iodine atoms replace the NO_2 groups, has been resolved.

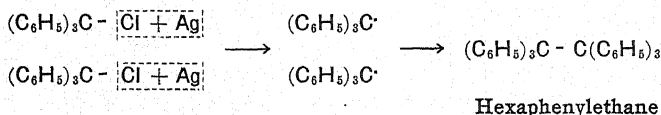
FREE RADICALS OF LONG LIFE

22-18 Triphenylmethyl, $(\text{C}_6\text{H}_5)_3\text{C}$. For nearly a half-century the principle of the Wurtz-Fittig reaction was applied to the synthesis of many different compounds without furnishing any trace of the free radicals assumed in explaining its mechanism. Invariably, the product obtained was the substance to be expected if these radicals united in pairs, *e.g.*,

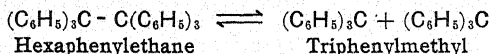


The tetraphenylethane resulting from this reaction is a colorless solid (m.p. 209°C) which boils without decomposition at 383°C . It is not affected by exposure to air or other mild oxidizing agents and, like most hydrocarbons of high molecular weight, is rather inert toward chemical agents in general.

Applying the same principle, Gomberg in 1900 undertook to prepare *hexaphenylethane* by treating a benzene solution of triphenylchloromethane with finely divided silver:



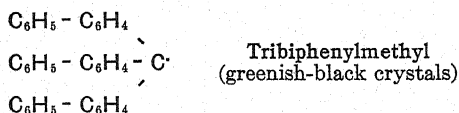
He naturally expected to obtain a colorless, rather inert substance resembling tetraphenylethane. He actually found that the benzene solution acquired a deep-yellow color and contained some substance which greedily absorbed oxygen when exposed to air, rapidly added iodine, and, in general, exhibited a remarkable and totally unexpected reactivity! In his own words: "In order to account for this unusual behavior, the plausible hypothesis was finally formulated that the two groups, $(\text{C}_6\text{H}_5)_3\text{C}$, failed to unite with each other or, if union had occurred, then spontaneous reverse dissociation was also taking place until an equilibrium was established."



Subsequent work of many chemists has fully justified this conclusion. By evaporation of the solvent in the absence of air, it is possible to isolate hexaphenylethane as a colorless solid, reasonably stable in sealed tubes. When dissolved in benzene or other anhydrous solvent, it yields solutions which are colorless at first but which quickly turn yellow and exhibit the high chemical reactivity that so surprised Gomberg.

The present-day student, having been introduced to the concept of free radicals early in his study of organic chemistry, may find it hard to understand either Gomberg's surprise or the epoch-making nature of his discovery. One has to realize that, from the days of Kekulé, the entire structural theory of organic chemistry had rested upon the supposition that *carbon always has a valence of four*. (The anomalous case of carbon monoxide was recognized but not permitted to interfere with faith in "the constant quadrivalence of the carbon atom.") The discovery of triphenylmethyl was the first proof that there could exist a substance in which a carbon atom exhibits the valence of *three*. Gomberg's announcement in 1900 startled organic chemists generally and, at first, was received with incredulity. One should realize also that this was years before the electron was recognized as having any role in organic chemistry—and that it was not until 1929 that Paneth obtained evidence for the actual, though very transitory, existence of *alkyl* free radicals (Sec. 2-7).

22-19 Triarylmethyl Free Radicals. Since Gomberg's observation there have been prepared several hundred different compounds that are more or less extensively dissociated into radicals containing tervalent carbon. Most of these are *hexaarylethanes*, of the type $\text{Ar}_3\text{C} \cdot \text{CAr}_3$. In general, they are colorless or faintly colored in the solid state but yield deeply colored solutions containing free radicals. Dissociation into free radicals varies widely with the nature of the aryl groups. It is favored by nitration of the phenyl groups, by the attachment of methyl groups (especially in *ortho* positions), and by replacing phenyl by naphthyl and biphenyl groups, $-\text{C}_6\text{H}_4 \cdot \text{C}_6\text{H}_5$. For example, it is believed that

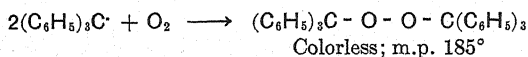


exists *only* in the form of free radicals and is incapable of associating to a corresponding hexaarylethane. In short, we are dealing here with a long-lived chemical individual containing a carbon atom with a valence of three. This is a "far cry" from the transitory methyl and ethyl free radicals described in Section 2-6 and the others which are formed as intermediate stages in many chemical reactions.

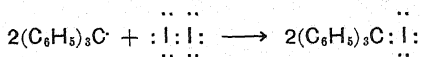
Apparently all *molecules* of the type $\text{Ar}_3\text{C} \cdot \text{CAr}_3$ are colorless. Hence, the appearance of color, in solution or otherwise, is regarded as an indication of dissociation into free radicals. The most reliable method for

estimating the degree of dissociation is based upon the fact that free radicals, because they contain unpaired electrons, are paramagnetic (*i.e.*, are attracted by a magnet). This *magnetic susceptibility* can be measured.

Reactions. All triarylmethyl radicals enter readily into various reactions in which the odd electron becomes paired and the tertiary carbon atom is restored to its normal valence of four. These include the addition of atmospheric oxygen to form peroxides:



and the addition of free halogens, *e.g.*,



They also react with the free alkali metals and with their amalgams:



When the hexaarylethanes are dissolved in liquid sulfur dioxide, they give solutions which conduct an electric current. Apparently the reaction is of the type



or

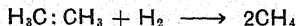


The anion $(\text{C}_6\text{H}_5)_3\text{C:}^-$ is deep red; both the free radical and the cation $(\text{C}_6\text{H}_5)_3\text{C}^+$ are yellow to the eye but give different absorption spectra.

22.20 It remains to explain why hexaarylethanes dissociate into triphenylmethyl free radicals. Qualitatively, one is disposed to say immediately that it must be due to a *weakened* bond between the tertiary carbon atoms, and this assumption is supported by quantitative evidence. As against the calculated 85 kcal per mole absorbed in the *thermal* dissociation of ethane



only about 11 kcal is required for hexaphenylethane. Also, the calculated heat of hydrogenation of ethane

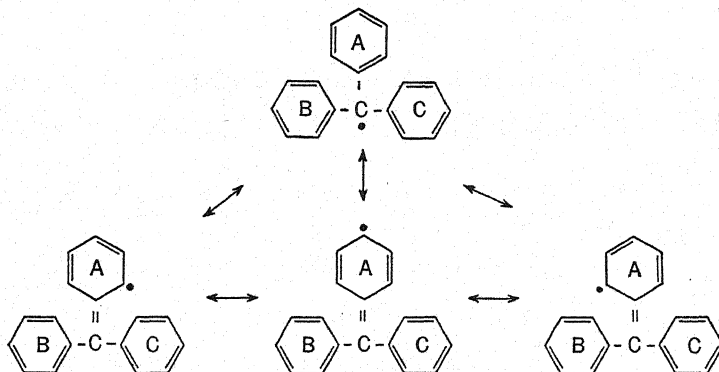


is some three times that measured for its hexaphenyl derivative. But *why* is the bond weaker?

An early explanation was based on *steric hindrance*—that is, the conception that there is not enough space about the two ethane carbon

atoms to permit the packing in of six aryl radicals without creating a strain which tends to force them apart. This is supported by evidence such as the greater dissociation when methyl groups occupy *ortho* positions and the fact that *alpha*-naphthyl groups promote dissociation more than *beta*. But it cannot be the entire explanation; for example, tetraphenylmethane, $(\text{C}_6\text{H}_5)_4\text{C}$, in which *four* phenyl groups are packed about a single carbon atom, is extremely stable and shows no indication of dissociating into free radicals. The current view is that steric effects do play a part but that this explanation, by itself, is inadequate.

Probably the major factor in dissociation is *stabilization of free triaryl-methyl radicals through resonance*. The twin molecule, $(\text{C}_6\text{H}_5)_3\text{C}\cdot$ $\text{C}(\text{C}_6\text{H}_5)_3$, is itself stabilized by resonance among the Kekulé forms which are possible for each of its phenyl groups, but there can be no interaction between its separate rings. Once the free radical is formed, however, there is not only resonance among the Kekulé forms but among many others. For example, in the triphenylmethyl free radical, the lone electron tends toward occupying each of 10 different positions. Four of these contributing forms are shown below, and there are three additional ones for each of the rings B and C:



The greater dissociation observed when phenyl groups are replaced by naphthyl and biphenyl groups is in conformity with this theory, for these latter provide still more resonance forms and, consequently, yield more highly stabilized free radicals. Resonance also seems adequate to explain the observed *color* of free radicals, as contrasted with the colorless hexa-arylethanes (Sec. 25.4).

Questions

1. List in separate series, and in the approximate order of decreasing effectiveness, the more important *meta*-directing and *ortho*-and-*para*-directing groups (cf. Sec. 5.19).
2. If a good yield of a single product is to be expected in the following reactions,

show its structure; otherwise, show the main components of the mixed product: (a) *p*-xylene is mononitrated; (b) 3-nitrobenzoic acid is monosulfonated; (c) salicylic acid is mononitrated; (d) *p*-nitroaniline is monochlorinated.

3. Which of the following compounds should give on nitration a better yield of 1-chloro-2,4-dinitrobenzene, *o*-Cl.C₆H₄.NO₂ or *p*-Cl.C₆H₄.NO₂. Explain.

4. In both of the sequences shown in Fig. 22-2, reduction follows oxidation and not conversely. Explain why this is important, quite aside from any matter of directing influences (Sec. 13-15).

5. The following compounds are not industrial products. Give series of reactions by which they can be made in the laboratory from benzene or chlorobenzene: (a) *m*-dichlorobenzene; (b) 1-chloro-3,5-dinitrobenzene.

6. Assuming that 1-chloro-3,5-dinitrobenzene were available industrially, explain why it would be less useful in chemical syntheses than its isomer 1-chloro-2,4-dinitrobenzene.

7. Using general methods, write structural equations for the reactions necessary in making the following compounds from chlorobenzene. Note carefully the effects of directing influence and choose the sequence of reactions in the order necessary to secure good yields of the desired products: (a) *p*-chloroaniline; (b) 2,5-dichloroaniline; (c) 2,4-dinitrophenol; (d) 4-chloro-2-nitroaniline; (e) 2-chloro-4-nitroaniline; (f) 3,4-dichloronitrobenzene; (g) 1-chloro-2,4-dinitrobenzene; (h) 4-amino-3-nitrobenzenesulfonic acid; (i) 2-chloro-5-aminobenzenesulfonic acid; (j) 4-chloro-3,5-dinitrobenzenesulfonic acid.

8. Show with the aid of formulas similar to (I) to (V) of Section 22-7 why the amino group of aniline is *ortho*- and *para*-directing and strongly activates these positions.

9. Show with the aid of formulas similar to (I) to (V) of Section 22-8 why the COOH and SO₃H groups are *meta*-directing and deactivating.

10. It is much easier to restrict to monosubstitution the Friedel-Crafts reaction of acetyl chloride with benzene than the corresponding reaction of methyl chloride. Explain.

11. Explain accurately: (a) why *p*-cresol is acidic while its isomer benzyl alcohol is a neutral compound; (b) why resonance in the anion of *p*-cresol is greater than in the parent molecule.

12. Aniline is a base, though a weak one. Explain why acetanilide shows substantially no basic properties.

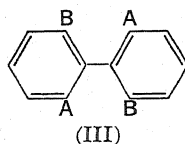
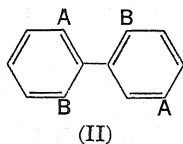
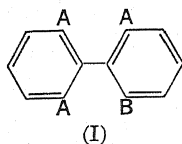
13. Correlate the low reactivity of the halogen atom in chlorobenzene with that in vinyl chloride.

14. Explain how a knowledge of the structures of aspirin and oil of wintergreen make possible accurate predictions as to their behavior in the bromine-water and ferric chloride tests and as to their solubilities in sodium hydroxide and sodium bicarbonate solutions.

15. Summarize the facts concerning the rates of formation and hydrolysis of the esters of 2,6-disubstituted benzoic acids, including their formation through silver salts, and explain in terms of space effects.

16. (a) Explain in terms of space effects the existence of optically active substituted biphenyls. (b) Optically active biphenyls, such as (II) of Section 22-17, are always obtained as racemic mixtures; why is it advantageous that they contain one or more carboxyl groups in order that these mixtures may be resolved?

17. Assume that A and B represent COOH and NO₂ groups, respectively. Which of the following would be expected, and which could not be expected, to give optically active isomers:



18. (a) Outline the principle of Gomberg's method for preparing triarylmethyl free radicals. (b) Why did he find it necessary to work with anhydrous solvents and in an atmosphere of an inert gas such as nitrogen?

19. (a) Summarize the structural conditions which favor the existence of free radicals of long life. (b) Why are steric effects inadequate to explain the independent existence of triarylmethyl free radicals? (c) Offer an explanation in terms of resonance, giving a specific illustration in detail.

CHAPTER 23

POLYFUNCTIONAL AROMATIC COMPOUNDS

II. PRODUCTS OF BENZENE

Polysubstituted and mixed aromatic compounds containing a single benzene nucleus number tens of thousands, and hundreds are industrial products. Structurally, most of them can be classified as derivatives of benzene or toluene, and practically, nearly all of them are made from these two hydrocarbons either directly or indirectly.

Figure 23-1 includes all the important compounds manufactured *directly* from benzene—that is, by a single reaction. The number is surprisingly small in comparison with the hundreds just referred to. The many others are produced by further chemical reactions from these initial products and from such “second-generation” descendants as phenol and aniline.

TABLE 23-1 PRODUCTS OF BENZENE MANUFACTURED IN LARGEST QUANTITIES; USA, 1950

Product	Millions of Pounds
Aniline.....	98
BHC (benzene hexachloride).....	77
Chlorobenzene.....	366
2,4-D and esters.....	28
DDT.....	78
<i>o</i> -Dichlorobenzene.....	17
<i>p</i> -Dichlorobenzene.....	45
Nitrobenzene.....	132
Phenol (synthetic).....	292
Styrene.....	539

23-1 Intermediates; Finished Products. Products manufactured by *chemical reactions* from benzene, toluene, and naphthalene are classified as intermediates or as finished products according to their major uses. Those used mainly for further chemical operations are *intermediates*. Nitrobenzene is a typical example; manufacturers sell only a small fraction of the large amount they produce, the major portion being reduced at once to aniline. Those substances with properties which give them value outside chemical industry and are sold for use by the general public are called *finished products*. These enter into general consumption as dyes, medicinals, perfumes, plastics, etc.

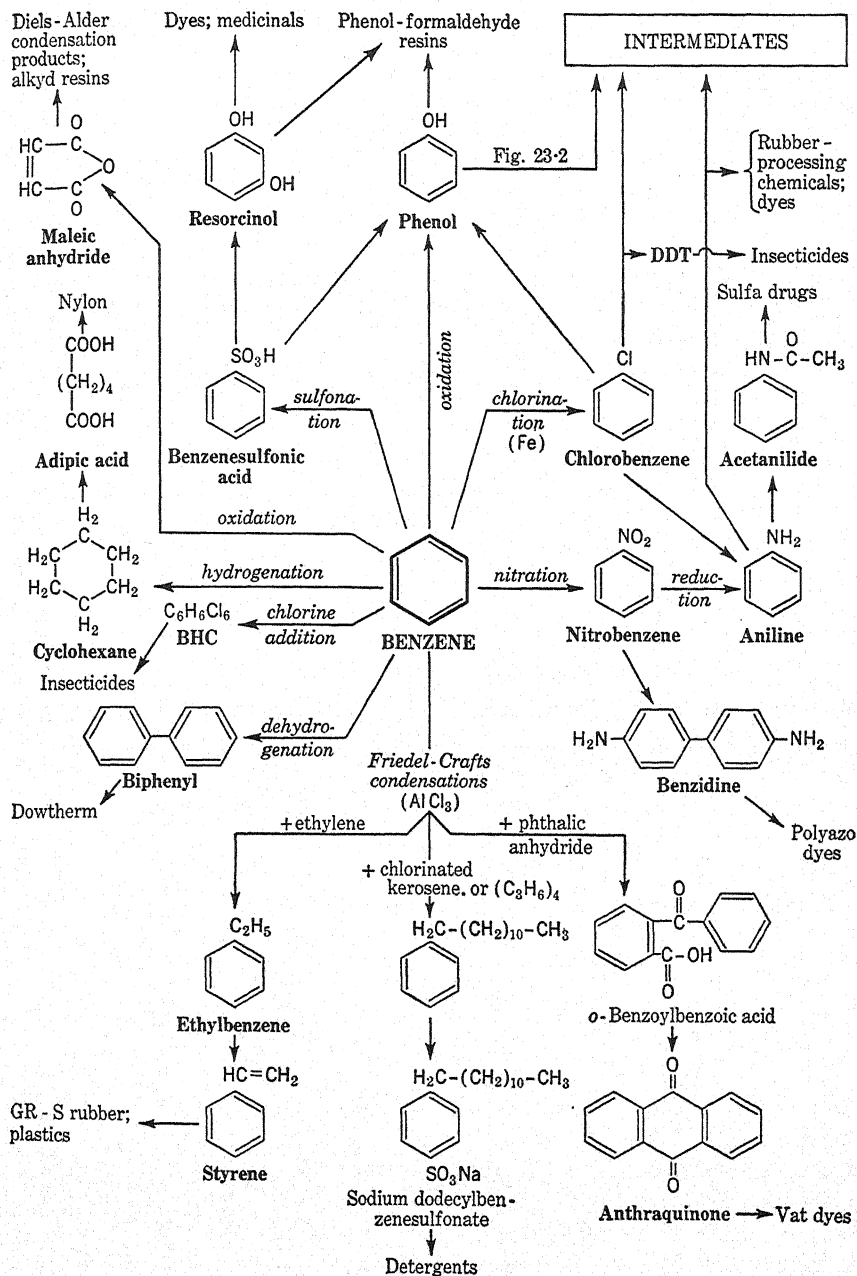


FIG. 23-1 The relations between benzene and the major compounds produced directly from it; a few further intermediates are included and their diversified end uses indicated.

This classification is useful but somewhat arbitrary; sharp dividing lines are hard to find. About 5 per cent of the purified acetanilide produced is used as such for medicinal purposes and, to this extent, it is a finished product; but the larger portion serves as an intermediate for the production of sulfa drugs, etc. Again, phenol is a crude, so far as concerns the relatively small amount which is isolated from coal tar. It is a finished product when put into use as an antiseptic or disinfectant. But phenol is classified as an intermediate because the great bulk of it is produced by chemical reactions and consumed in other chemical reactions such as the manufacture of plastics.

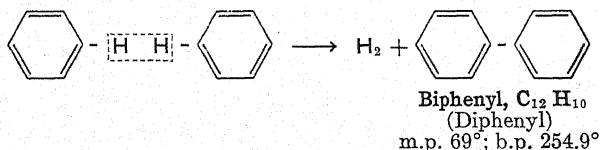
23-2 Benzene Hexachloride. In the presence of short-wave radiation and in the absence of catalysts favoring nuclear substitution, benzene adds three molecules of chlorine:



This addition product, which is commonly called benzene hexachloride (or BHC, in the insecticide industry), is properly described as 1,2,3,4,5,6-hexachlorocyclohexane. It is manufactured extensively, for use as an insecticide against the cotton boll weevil and other agricultural pests.

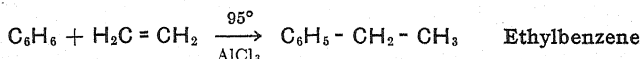
The product obtained by the addition of chlorine to benzene is a mixture of four of eight possible geometrical isomers, differing in the positions of Cl and H atoms above and below the plane of the carbon ring (Sec. 17-17). Only one of these, the so-called *gamma* isomer, which composes 10 to 12 per cent of the product, has marked insecticidal properties. The mixture is generally sold and used without separation, but increasing amounts of the *gamma* isomer (m.p. 111°C) are being concentrated by fractional crystallization and sold as Lindane. We do not know either the geometrical configuration of Lindane or why it alone is especially active toward insects.

23-3 Biphenyl is manufactured by bubbling the vapors of benzene through molten lead (m.p. 327.5°C) containing catalysts:

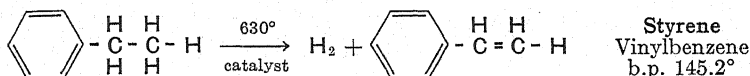


This hydrocarbon is highly stable even at temperatures well above its boiling point. Its major use is in admixture with phenyl ether as an indirect heating medium for operations which must be conducted at high but controlled temperatures (Dowtherm, Sec. 9-10). The *o*- and *p*-hydrogen atoms enter readily into the benzene substitution reactions, and various nitro compounds, sulfonic acids, and halogen substitution products are thus obtained. The optical activity of some substituted biphenyls was described in Section 22-17.

23.4 Styrene is the intermediate produced from benzene in the largest amount. The first step is alkylation with ethylene:



A little ethyl chloride is fed in with the ethylene; this furnishes HCl (together with ethylene) which acts as a catalyst promoter. The alkylation can be effected also with phosphoric acid as catalyst. In a second operation, ethylbenzene is converted into styrene by catalytic dehydrogenation over a solid catalyst in the presence of superheated steam:



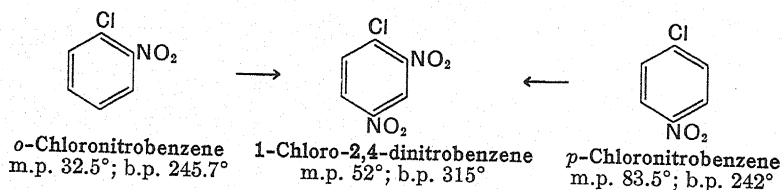
Styrene is highly reactive in all alkene addition reactions. Addition polymerization—on which most of its industrial use depends—occurs spontaneously and must be prevented during shipment and storage of the monomer by the addition of a small amount of an inhibitor (*tert*-butylcatechol, a readily oxidizable phenol). The use of large quantities of styrene in the manufacture of GR-S synthetic rubber by copolymerization with butadiene was described in Section 6-17.

Polystyrene. Comparably large amounts of styrene are used for manufacturing polystyrene, one of the major thermoplastic resins. Polystyrene is a water-white, transparent substance which softens slightly above 100°C and becomes a viscous liquid around 185°C. It is an excellent electrical insulator and highly resistant to water and most chemicals; thus it is used in the manufacture of electrical parts, storage-battery boxes, screw tops for acid bottles, etc. Commercial grades (Styron) usually have an average molecular weight of the order of 60,000 to 120,000, corresponding to the union of some 600 to 1200 molecules of styrene.

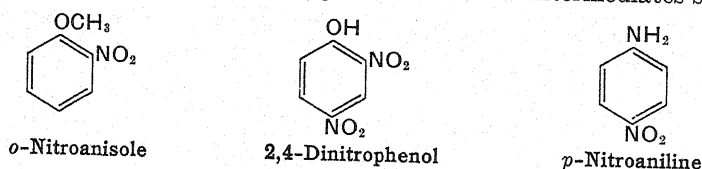
PRODUCTS OF CHLOROBENZENE

23.5 Nitro-halogen Compounds. The major part of the large amount of chlorobenzene manufactured is used for conversion into phenol and aniline as previously described. In these operations the low reactivity of the halogen atom is overcome by high temperatures obtainable only in special pressure equipment (cf. Sec. 8-31). Most of the remaining chlorobenzene is nitrated.

On nitration with mixed acid in the usual way, chlorobenzene yields a mixture of *o*-chloronitrobenzene and *p*-chloronitrobenzene (in the proportion of about 30 to 70) which is separated by fractional crystallization. With more concentrated acid either compound, or the mixture of the two, yields 1-chloro-2,4-dinitrobenzene:

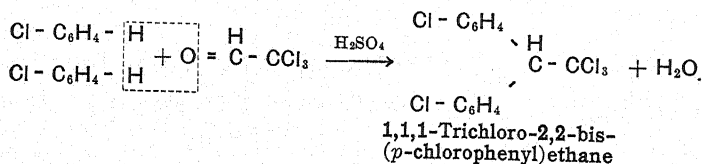


The activating effect of nitro groups in the *ortho* and *para* positions (Sec. 22.13) makes it possible to replace the chlorine atoms in these compounds under ordinary factory and laboratory conditions. Thus, replacements by OCH_3 , OH , NH_2 , etc., yield other useful intermediates such as



Two military high explosives, picric acid and tetryl, are manufactured from 1-chloro-2,4-dinitrobenzene. Reduction of the NO_2 group to NH_2 converts *o*-nitroanisole into *o*-anisidine.

23.6 DDT. Chlorobenzene readily condenses in the *para* position with chloral:



The product, originally prepared in 1874, became of interest around 1939 when its value as an insecticide was first recognized. It is now manufactured and used in large quantities against flies, moths, agricultural pests, and in area spraying from airplanes to control malaria-bearing mosquitoes. The popular abbreviation, DDT, is derived from the alternate chemical name, *dichlorodiphenyltrichloroethane*. The reaction of formation, which is the one used in manufacturing, illustrates a quite common condensation between aldehydes and nuclear hydrogen atoms of benzene derivatives.

23.7 Benzene Polyhalides. All the polyhalides theoretically obtainable from benzene by replacing two to six hydrogen atoms by as many atoms of chlorine, bromine, or iodine have been prepared. Many mixed halides containing two or more of these halogens, and some with fluorine, are also known. The most important are *o*- and *p*-dichlorobenzene. A mixture of these compounds, containing chiefly the *para* isomer, is obtained regularly as a by-product of the manufacture of chlorobenzene

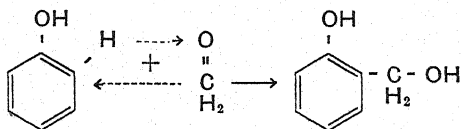
(Sec. 7-20) and can be made the major product, when desired, by chlorination of benzene in the presence of aluminum chloride. The *para* compound is symmetrical and has the higher melting point (53°C), a property which is utilized in separating it, by chilling, from the liquid *ortho* isomer (m.p. -17.6°C). *p*-Dichlorobenzene is replacing naphthalene as a moth repellent and is used also against the peach-tree borer and for making a few intermediates. The *ortho* compound is used principally as a solvent.

Further chlorination of either dichlorobenzene or their mixture yields principally 1,2,4-trichlorobenzene—which is formed also when BHC is heated with an alkali. This compound is used in the control of termites and in compounded transformer oils. Tetrachlorobenzene (1,2,4,5) is also manufactured.

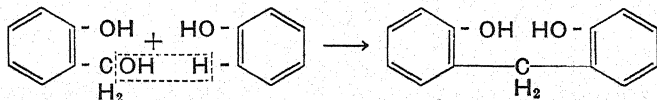
PRODUCTS OF PHENOL

It has been emphasized already that the hydroxyl group is one of the most powerful in activating the *ortho* and *para* positions of the aromatic nucleus toward attacks by electrophilic reagents (Sec. 22-7). Thus the *ortho* and *para* hydrogen atoms of phenol are easily replaced in all the ordinary substitution reactions of benzene and also in many others which either do not occur with aromatic hydrocarbons or are too slow to be useful. A number of these nuclear reactions are indicated in Figure 23-2, and some are described in more detail below.

23-8 Phenol-Aldehyde Resins. The largest use of phenol by far is in condensation with formaldehyde to produce resins of the Bakelite¹ type. This can be effected with the aid of either an alkaline or an acid catalyst. The initial reaction is addition of phenol, at one of its active *ortho* or *para* positions, to the carbonyl bond of formaldehyde:



This can occur at all three active positions of a phenol molecule and is accompanied by other condensations such as



¹ Named for the inventor, Leo H. Baekeland (1863-1944), a Belgian-born chemist who came to the United States as a young man. He is properly regarded as the father of the synthetic-plastics industry, which he started on a very small scale in 1907. Bakelite is now the trade-marked name for the products of one corporation. Similar phenol-aldehyde condensation products are manufactured by numerous other companies and marketed under a wide variety of trade names.

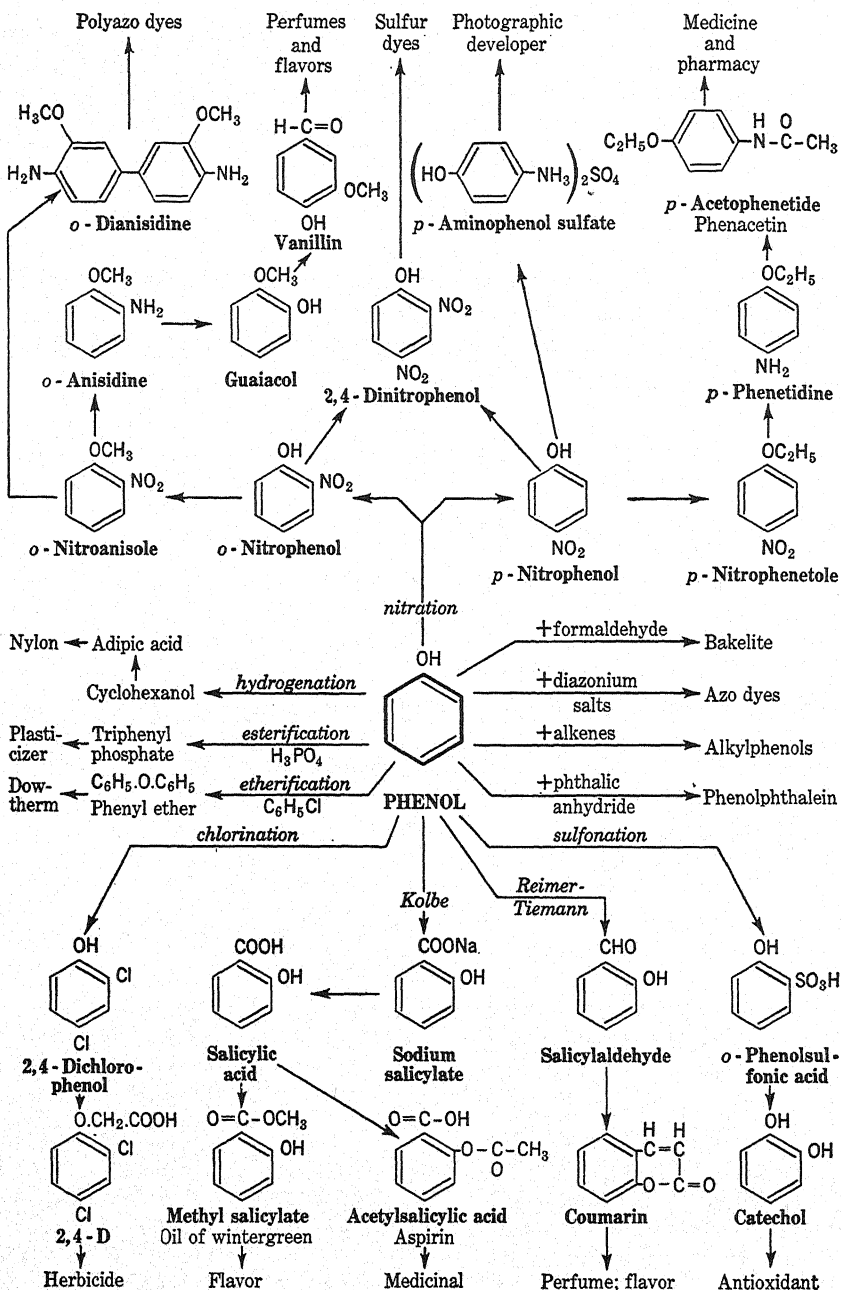


FIG. 23-2 The relations between phenol and some of the intermediates and finished products for which it is used.

Repetition of these reactions leads to a more and more complicated network of cross-linked chains such as is indicated in Figure 23-3 for a very small segment of the condensation polymer.

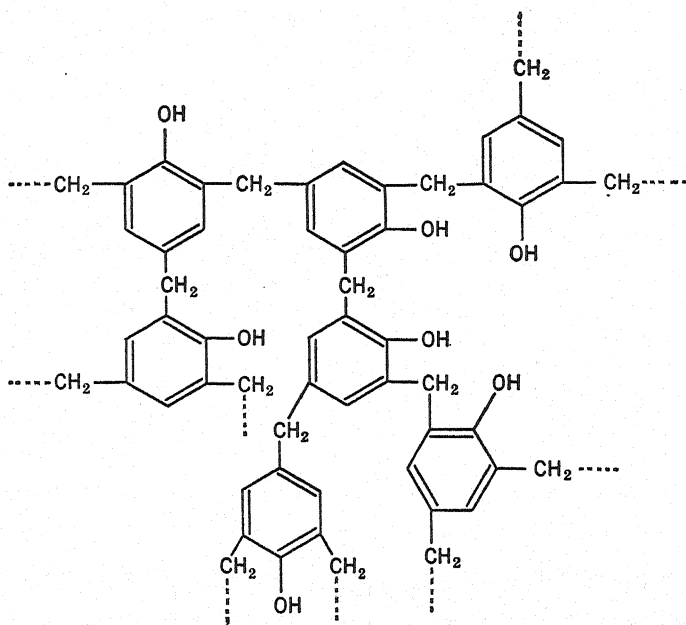


FIG. 23-3 Phenol-formaldehyde condensation resin; a small portion of the molecule. The *three* active positions on the phenol nucleus make possible the formation of cross linkages between linear chains. Such cross-linked, three-dimensional structures are not fusible.

The reaction is controlled in practice—*e.g.*, by the time and temperature of heating, the choice of catalysts, etc.—to give products called A, B, and C. Bakelite A is a product of low molecular weight formed during the earlier stages; it may be a solid, a semisolid, or a liquid and is *soluble in acetone* and some other organic solvents. Further heating yields a B resin, which is insoluble but remains plastic during a limited period of heat working. In all the practical applications (Sec. 23-9), an A- or B-stage resin is heated by the user and thus converted into the C stage, which is insoluble in all liquids and *cannot be melted or softened* by reheating.

This irreversible hardening by heat differentiates *thermosetting* resins from thermoplastics such as the polyvinyls and polystyrene. It has been noted (Sec. 15-7) that thermoplastics consist of long, stringlike molecules with few if any cross linkages; such molecules slip over each other when heated, and the material softens or may melt, as does nylon. The

irreversible setting ("curing") of a phenol-aldehyde resin by heat results from the formation of many cross linkages between chains, giving a tightly bound, three-dimensional structure. The alkyd resins (Sec. 24.14) also are thermosetting.

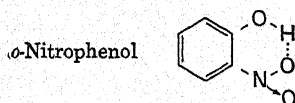
Phenol and formaldehyde remain the major materials for the manufacture of phenol-aldehyde condensation resins. The properties of the products are often modified, however, by substituting for part of the phenol a mixture of the cresols or, for certain purposes, other phenol homologues or resorcinol. Furfural (Sec. 26.10) is used to a limited extent in place of formaldehyde.

23.9 The largest use of the bakelite-type plastics is in manufacturing *molded* objects. A suitable resin of the A or B stage is mixed intimately with a filler and, usually, a pigment. The mixture is compressed at 2000 to 5000 psi in a mold having the desired shape, with simultaneous heating (130 to 180°C) until "curing" is complete. Telephone desk sets and innumerable other objects are molded in this way. The resin usually makes up 25 to 50 per cent of the molding powder; the filler is commonly wood flour, but this may be replaced wholly or in part by cotton linters, asbestos fibers, etc. The physical properties of the molded article are largely determined by the nature and amount of the filler, the pure resin being so brittle as to be almost useless.

Another extensive use of these resins is in the manufacture of *laminated* materials. Layers of paper, cloth, asbestos paper, glass fabric, etc., are impregnated with the solution of an A-stage resin, laid one upon another to build up the desired thickness, and bonded into a unit by heating under great pressure. Waterproof plywood is made similarly by bonding thin sheets of wood. *Cast* articles are made by pouring a suitable resin—not containing a filler—into molds; color can be imparted by incorporating oil-soluble dyes, and mottled effects are obtained by the use of pigments. Combs, buttons, costume jewelry, small radio cabinets, etc., are made in this way. Another minor use is in surface coatings such as spar varnishes and paint vehicles.

23.10 Nitrophenols. When phenol and dilute (20 per cent) nitric acid are mixed, with cooling to absorb the heat of reaction, the product consists of about equal parts of *o*-nitrophenol and *p*-nitrophenol and some tarry oxidation products. Separation is effected by steam distillation, *o*-nitrophenol alone being volatile. Pure *p*-nitrophenol crystallizes in colorless needles (m.p. 114°C) which sublime when strongly heated; *o*-nitrophenol forms canary-yellow crystals which melt at 45°C and boil at 214.5°C.

The different volatility of these isomers is explained by *internal* hydrogen bonding in the *ortho* compound, which has the chelated structure



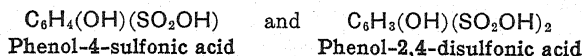
Thus molecular association does not take place. Space relations prevent

chelation in *p*-nitrophenol, which is associated like other phenols and alcohols through hydrogen bonding between different molecules.

Further nitration leads to 2,4-dinitrophenol and *picric acid*, 2,4,6-trinitrophenol. The latter was formerly a military high explosive and its salt, ammonium picrate, is still used in armor-piercing shells because it does not explode immediately on impact. This insensitiveness to shock is in striking contrast with the behavior of lead, copper, and other *metallic* picrates, which are detonated so easily that handling them is highly dangerous. Picric acid likewise forms salts with organic bases and forms addition complexes, also called picrates, with aromatic hydrocarbons.

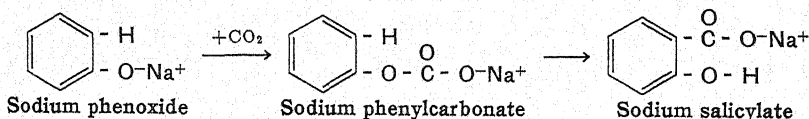
The action of nitric acid on phenol is rapid and highly exothermic. The heat evolved in large-scale nitrations cannot be removed fast enough to prevent rise in temperature and a further increase in rate of reaction. Thus it is difficult to stop short of picric acid and impossible to avoid losses through the *oxidation* of phenol to tars and reduction of nitric acid to NO and NO₂, which escape. For these reasons the chloronitrobenzenes often afford the best route to nitrophenols. Picric acid can be made in good yield by nitrating 2,4-dinitrophenol, obtained from 1-chloro-2,4-dinitrobenzene.

When it is desired to nitrate phenol directly to picric acid, it is first sulfonated to a mixture of



and then nitrated with mixed acid. The deactivating SO₃H groups slow the reaction so that undue rise in temperature is avoided. After one nitro group has entered, SO₃H groups are gradually replaced by NO₂. Protection of phenols against oxidation in laboratory operations, by methylation of the OH group, was described in Section 9.9.

23.11 Salicylic Acid; Kolbe Synthesis. Salicylic acid (*o*-hydroxybenzoic acid) is the most important carboxylic acid containing a phenolic hydroxyl group. It occurs in oil of wintergreen and oil of birch as its methyl ester and is manufactured from phenol by the *Kolbe synthesis*. This procedure, as improved by Schmidt, consists in saturating dry sodium phenoxide with carbon dioxide and then heating under pressure at 120 to 140°C; the product is sodium salicylate. It is usually assumed that carbon dioxide is absorbed to form sodium phenylcarbonate and that, when this is heated, the COONa group exchanges place with one of the activated *ortho* hydrogen atoms:

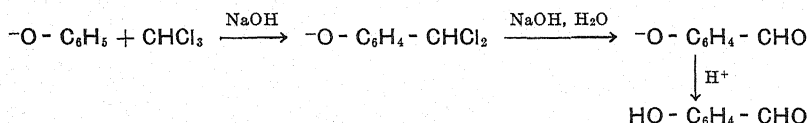


An alternate possibility is that the phenoxide ion, acting as a carbanion derived from one of its resonance forms (Sec. 22.11), adds directly to the

carbon atom of carbon dioxide. The Kolbe-Schmidt reaction can be used to introduce the COOH group (carbonation) into other phenols and into naphthols.

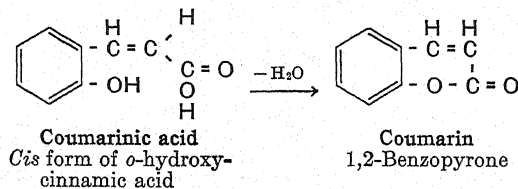
Salicylic acid and some of its salts and esters are used medicinally. Its largest use is for the manufacture of acetylsalicylic acid, aspirin, which is produced in larger quantities than any other medicinal compound. The relations between salicylic acid, aspirin, and methyl salicylate were discussed in Section 22-10.

23-12 Salicylaldehyde (*o*-hydroxybenzaldehyde) is a fragrant plant product which is synthesized by heating phenol with chloroform and sodium hydroxide solution. Probably an intermediate is the dichloride, which is hydrolyzed to the aldehyde group like benzal chloride:

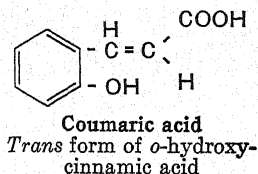


At the end of the reaction the mixture is acidified and steam distilled. In this way the *ortho* compound, which is volatile with steam, is separated from the nonvolatile *para* isomer which is also formed to some extent. This method for preparing phenolic aldehydes is known as the *Reimer-Tiemann* reaction.

Coumarin is a cyclic ester or lactone which can be made from salicylaldehyde by heating with acetic anhydride and potassium acetate (Perkin reaction, Sec. 15-22). It is usually assumed that an intermediate product is *coumarinic acid*, which immediately loses water to form coumarin:



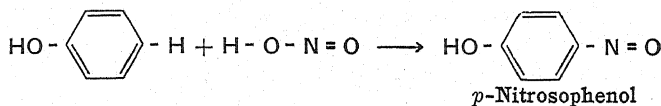
The *trans* isomer, *coumaric acid*, can be made and does not form a lactone. Restriction on revolution, due to the double bond, prevents the COOH and OH groups from approaching and reacting with each other.



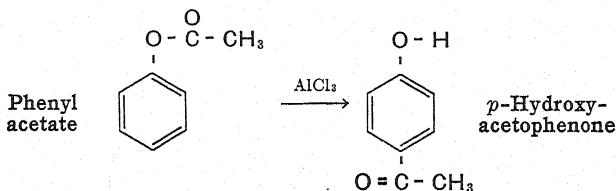
Coumarin is the odoriferous substance of the tonka bean. It is used extensively in food flavors (sometimes as a vanilla substitute), in perfumes, and in the manufacture of cigarettes and smoking tobacco.

23-13 Some other reactions of phenols which involve the special reactivity of positions *ortho* or *para* to the hydroxyl group include the following:

Nitrosation. Phenol reacts with nitrous acid to give a *p*-nitroso-derivative (cf. footnote page 462):



Fries Reaction. When a phenolic ester is heated with aluminum chloride, it is converted into an isomeric hydroxy ketone in which the acyl group has migrated to an *ortho* or a *para* position:



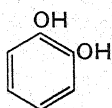
Usually, both the *ortho* and *para* compounds are formed, and the reaction is useful in preparing hydroxy ketones of these structures. Migration to a *meta* position has not been observed.

Alkylation. Various homologues of phenol, containing alkyl side chains of up to nine or more carbon atoms, are manufactured by alkylation with alkenes. Thus isobutene gives *p*-*tert*-butylphenol. These reactions, in the activated positions, occur more easily than with benzene and other aromatic hydrocarbons; sulfuric acid is a satisfactory condensing agent.

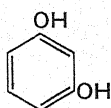
POLYHYDRIC PHENOLS

Departing from the general plan of this chapter, polyhydric phenols are described at this point although they are not produced from hydroxybenzene. Structurally, however, all may be regarded as its derivatives.

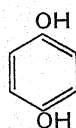
23-14 Dihydric Phenols. The most important of these are the three isomeric dihydroxybenzenes:



Catechol
m.p. 105°; b.p. 245°



Resorcinol
m.p. 110°; b.p. 280°



Hydroquinone
m.p. 170.5°; b.p. 286.2°

The usual effects of introducing hydroxyl groups are seen in the facts that these compounds are solids, melting and boiling at higher temperatures than the monohydric phenols and considerably more soluble in water. In most chemical properties they closely resemble the monohydric phenols. They give deeply colored solutions with ferric chloride, and nuclear hydrogen atoms are readily substituted by chlorine and bromine. They form ethers and esters by the usual reactions of the hydroxyl hydrogen atoms. Catechol, hydroquinone, and other phenols containing OH groups *ortho* or *para* to each other are noteworthy for the ease with which they are oxidized.

23·15 Resorcinol, 1,3-dihydroxybenzene, is manufactured by the further sulfonation of *meta*-directing benzenesulfonic acid, followed by alkali fusion. It is an intermediate for a few dyes, and a dilute water solution is used for disinfecting the skin. *Hexylresorcinol*, a derivative of greater importance for the latter purpose, contains the *n*-hexyl radical in the 4 position. This position is highly activated by both OH groups, and resorcinol readily condenses with *n*-caproic acid in the presence of anhydrous ZnCl_2 (a mild Friedel-Craft type reagent). The ketone $(\text{HO})_2\text{C}_6\text{H}_3\text{CO}\cdot\text{C}_6\text{H}_{11}$ thus obtained is reduced to $(\text{HO})_2\text{C}_6\text{H}_3\cdot\text{C}_6\text{H}_{13}$ by the Clemmensen method. The largest use of resorcinol is in aldehyde condensation resins for bonding plywood (Sec. 23·9).

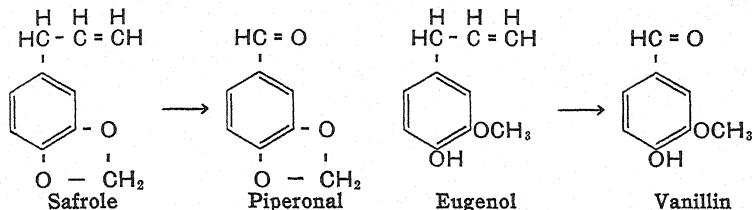
23·16 Catechol, 1,2-dihydroxybenzene, is manufactured by high-pressure alkaline hydrolysis of *o*-dichlorobenzene and by alkali fusion of sodium *o*-phenolsulfonate. Its reducing action (cf. hydroquinone, below) makes it useful as a photographic developer and as an antioxidant in gasoline. Similarly its derivative *tert*-butylcatechol is added to styrene monomer to inhibit polymerization.

The original source of catechol was its monomethyl ether *guaiacol* (b. p. 205°C) which is the chief component of that fraction of beechwood tar distilling at 200 to 205°C , called beechwood creosote. Guaiacol is readily converted into catechol by the action of HI or AlCl_3 .

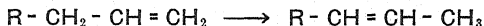
Catechol derivatives occurring in plants in useful quantities include eugenol, safrole, and vanillin. *Safrole*, the chief component of oil of sassafras, is a liquid boiling at 234.5°C . It can be oxidized to the aldehyde piperonal, which is used as a perfume under the name heliotropin. It will be noted that both safrole and piperonal are cyclic ethers derived from catechol.

Eugenol, the principal component (85 to 95 per cent) of oil of cloves, is used mainly for the manufacture of *vanillin*. During the necessary oxidation of the side chain, the nucleus is protected by acetylating the hydroxyl group. Vanillin is also synthesized from guaiacol by the Reimer-Tiemann reaction. Vanillin is the substance mainly responsible for the flavor and odor of true "vanilla extract," which is prepared by

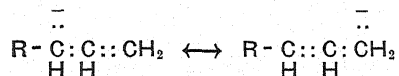
extracting the vanilla bean with alcohol. The synthetic product is one of the major raw materials of the perfume industry.



23-17 Shifting of Double Bonds. Eugenol and safrole each contain a double bond which, as usual, is sensitive to oxidation. But they do not readily yield the desired aldehydes (vanillin and piperonal), in which the CHO group is directly attached to the nucleus. Hence, in the manufacture of these compounds advantage is taken of the observation that, when heated under pressure with alkali solutions, eugenol and safrole are converted into isomeric compounds (isoeugenol and isosafrole), which are more readily oxidized to the desired aldehydes. In both cases the double bond is shifted to a position where it is conjugated with the benzene nucleus (conversion of an allyl into a propenyl side chain):



It is usually assumed that alkali removes a proton, forming a hybrid carbanion



to which a proton may add in either of two positions. When, as is most common, R is an aryl nucleus, the carbanion is further stabilized by resonance with the ring electrons. The allylic rearrangements referred to in Section 15-4 are regarded as taking place in a hybrid *carbonium* ion.

23-18 Hydroquinone, 1,4-dihydroxybenzene, is usually manufactured by reducing quinone (Sec. 23-20) with sulfur dioxide, a mild reducing agent. It is used extensively as a developer in photography. Hydroquinone itself and various derivatives (*e.g.*, the monomethyl ether and 2,5-di-*tert*-butylhydroquinone) are used also as antioxidants in rubber, fats and oils, etc., and as polymerization inhibitors in the monomers of synthetic resins such as acrylates and alkyds. Such uses depend on the ease with which these compounds react with and remove peroxides and free oxygen.

23-19 Photographic Developers. The light-sensitive emulsion of photographic film is composed of minute granules of silver bromide distributed in gelatin. The latter holds the silver salt on the backing of cellulose acetate and also increases its sensitivity. On exposure to light, during the instant the picture is "taken," *some* of the granules are superficially reduced in some way. The function of a developer is to complete reduction by converting into metallic silver those granules in which it has

been started by photochemical action. An ideal developer is one which affects *only* the light-struck granules, leaving the others to be dissolved out by sodium thiosulfate (*hypo*) in the subsequent operation of *fixing*. A developer is satisfactory in practice if, under the conditions of use, its action is much more rapid with the light-affected particles than with the others.

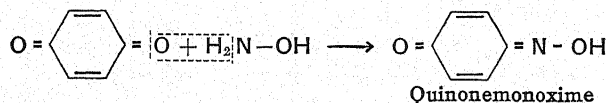
A photographic developer must be, therefore, an effective reducing agent which acts selectively. The two most widely used are hydroquinone and Metol (the sulfate of *p*-methylaminophenol). The developing bath is an alkaline solution containing also sodium carbonate, sodium sulfite, and potassium bromide. The developer is of course oxidized as the silver bromide is reduced, but not much is known about the complex organic compounds which are thus formed in the developing bath.

The amount of silver deposited in any section of a properly developed photographic negative depends on the number of individual silver halide granules in that area which were affected during the exposure. This, in turn, varies with the length of exposure, the intensity of the light, and the wave length of the light. Ordinary silver halide emulsions are much more sensitive to the short waves of the blue and violet than to the longer ones of yellow and red. Greater sensitivity toward the latter is secured by incorporating in the emulsion small amounts of certain dyes known as photographic sensitizers. The most important of these are cyanine dyes, highly colored compounds derived from quinoline (Sec. 26.4). The use of sensitizers is especially important in long-range photography where the shorter waves are largely absorbed by atmospheric haze.

23.20 Quinones. The oxidation of aniline with cold dichromic acid yields a product of the composition $C_6H_4O_2$ called *quinone* or, more accurately, *p*-benzoquinone. Quinone is manufactured in this way and used for reduction by sulfur dioxide to hydroquinone. The latter is easily oxidized to quinone by dichromic acid or sodium chlorate. This reversible reaction involves changes in structure which are much more deep-seated than most oxidation-reduction reactions.

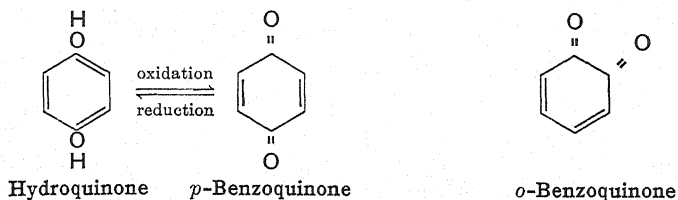
Quinone crystallizes in deep yellow needles (m.p. 115.7°C) which dissolve readily in ether and in alcohol. Unlike the nonvolatile, water-soluble hydroquinone it is only sparingly soluble even in hot water and is volatile with steam. Quinone forms a dioxime,¹ showing that it contains

¹ It also forms a monoxime:



This compound is interesting because it is identical with the product obtained by the action of nitrous acid on phenol (Sec. 23.13), thus indicating that it is a tautomeric substance. The actual structure of the crystals is not known.

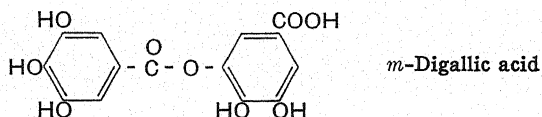
two carbonyl groups, and enters into various addition reactions characteristic of the ethylenic double bond. These properties are explained by the structural formula below, which pictures it as a diketocyclohexadiene:



This means that, when two hydrogen atoms are removed from hydroquinone by an oxidant, the typical aromatic or benzenoid structure is sharply altered and there develops a different conjugated system. The latter occurs in various compounds which are described as having the *quinoidal* structure. It usually results in the production of color. *o*-Benzoquinone, which is related to catechol as is quinone to hydroquinone, occurs in two crystalline forms, bright green needles and red plates. No *meta* quinone has ever been obtained. The general method for preparing quinones is the oxidation of aromatic compounds in which OH or NH₂ groups are *para* to each other.

23-21 Tannins; Gallic Acid; Pyrogallol. The term *tannin* describes a group of widely distributed vegetable products of somewhat variable composition. They dissolve in water to solutions of astringent taste which give blue-black or green colorations with ferric ions and are precipitated by solutions of gelatin and other proteins. They unite with rawhide to form *leather*. The chief sources are oak and hemlock bark and nut galls; the latter are excrescences produced by the sting of an insect on the leaves and young twigs of certain species of oak, particularly in the Orient. The natural tanning extracts, used in the manufacture of leather, are obtained by extracting these materials with water.

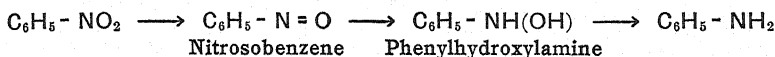
The substance commonly known as *tannic acid* or *gallotannin* is a colorless solid of high molecular weight. On hydrolysis it yields gallic acid and glucose in the proportions of ten molecules to one. It is probable that it is a glucoside in which each of the five hydroxyl groups of glucose is esterified by one molecule of a digallic acid:



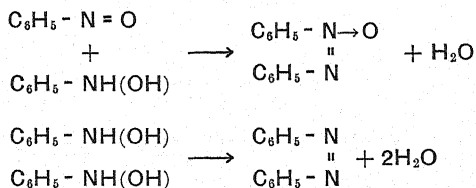
Gallic acid is used for the production of pyrogallol ("pyrogallic acid") which it yields on heating:

23-23 Intermediate Reduction Products. When nitrobenzene is reduced in the usual way, by the action of iron or tin and hydrochloric acid, it gives an almost quantitative yield of *aniline*. This change of NO_2 to NH_2 is not a single reaction but the over-all result of a series of successive reactions in which various intermediate reduction products are formed. With a metal and an acid, all these reactions proceed so rapidly that only aniline—the end product of the series—can be isolated. By changing the conditions, particularly the reducing agents used, it is possible to obtain good yields of intermediate reduction products. Some of these are compounds of considerable importance.

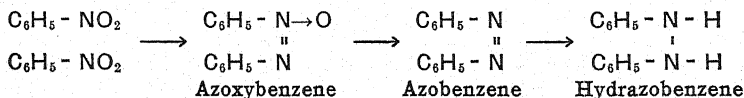
With substantially neutral reagents, reduction of a nitro group proceeds through the following stages:



In the presence of alkalis, nitrosobenzene and phenylhydroxylamine may react either with each other or with unaltered nitrobenzene to give products containing *two* phenyl radicals, *e.g.*,



At the same time, all intermediate products are subject to further reduction. The products ordinarily obtained by regulated *alkaline* reduction are related to each other as follows:

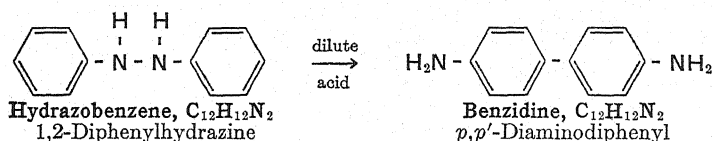


Nitrosobenzene (m.p. 68°C) is best obtained by the gentle oxidation of phenylhydroxylamine. It should be noted that it is *not* formed by the action of nitrous acid on benzene. *Phenylhydroxylamine* (m.p. 82°C) is best prepared by stirring nitrobenzene with a cold solution of ammonium chloride and zinc dust. *Azoxybenzene* (m.p. 36°C) is usually made by refluxing nitrobenzene with alcoholic potassium ethoxide; it crystallizes from hot alcohol in yellow needles. *Azobenzene* (m.p. 68°C) may be obtained: (a) by reducing nitrobenzene with alkaline sodium stannite; (b) by distilling azoxybenzene with iron filings; (c) by the oxidation of hydrazobenzene with ferric chloride or atmospheric oxygen. It crystallizes in orange leaflets.

Hydrazobenzene; Benzidine. Practically, hydrazobenzene is the most important of these intermediate reduction products. It is manufactured by stirring nitrobenzene, while boiling under reflux, with a solution of

sodium hydroxide and iron filings or zinc dust. Pure hydrazobenzene forms colorless crystals (m.p. 131°C) which readily turn orange or red on exposure to air through oxidation to azobenzene. The technical use of hydrazobenzene depends upon its rearrangement under the influence of dilute acids to benzidine, an important intermediate for polyazo dyes.

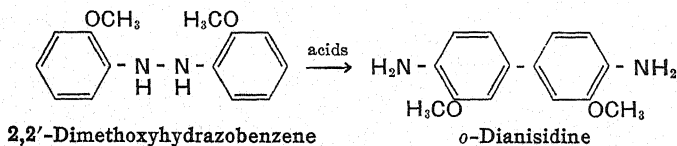
23-24 Benzidine Rearrangement. When warmed with dilute hydrochloric acid hydrazobenzene is converted irreversibly into its isomer, benzidine. The properties and structures of these two compounds may be summarized as follows:



Heat of combustion, 1597 kcal; m.p., 131° ; colorless crystals from alcohol, practically insoluble in water; lacks basic properties; oxidized by air to red azobenzene; cannot be diazotized and fails to give other amine reactions; nascent hydrogen converts it into two molecules of *aniline*, thus indicating that the two phenyl radicals are joined *through nitrogen* as indicated in the formula above.

Heat of combustion, 1561 kcal; m.p., 127° ; sparingly soluble in water; forms well-defined salts with acids, indicating basic properties; not oxidized by air; can be diazotized, and then couples with two molecules of phenols, showing two amino groups; when the dry diazonium salt is heated with alcohol *biphenyl* is obtained; this establishes the *direct* linkage of the two phenyl radicals.

This type of intramolecular change, known as the *benzidine rearrangement*, is common to many diarylhydrazines of the type Ar.NH.NH.Ar' . A further illustration is the reaction



The corresponding *ethyl* compound rearranges in the same way and at about the same rate, yielding *o*-diphenetidine.

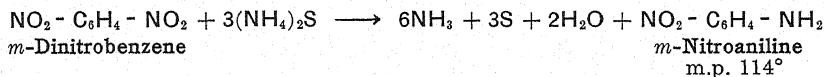
The following experiment furnishes convincing evidence that the benzidine change is a true *intramolecular* process in which the groups migrate without passing outside the sphere of molecular influence. Equimolar quantities of 2,2'-dimethoxyhydrazobenzene and of the corresponding *diethoxy* compound were mixed and treated with dilute acid. Each was rearranged as when treated alone, and there was no indication of the formation of a mixed compound containing one *methoxy* and one

ethoxy group. The formation of such a mixed compound would seem almost certain if the rearranging molecules were split into free radicals or other independent parts that subsequently recombined in another way.

23-25 *m*-Dinitrobenzene is manufactured by the further nitration of $C_6H_5.NO_2$. Deactivation by the NO_2 group already present makes it necessary to use a more concentrated mixed acid and a higher temperature (around $115^\circ C$). The nitro group is not exclusively *meta* directing, and small amounts of the *ortho* and *para* isomers are formed. Pure *m*-dinitrobenzene is obtained in faintly yellow crystals (m.p. $89.7^\circ C$) by crystallization from benzene or toluene. It is used for making *m*-phenylenediamine and *m*-nitroaniline.

m-Phenylenediamine (*m*-diaminobenzene) is made by reducing *m*-dinitrobenzene with iron and hydrochloric acid. The free base (m.p. $62.8^\circ C$) is quite soluble in water and readily oxidizes in alkaline solutions. For these reasons it is usually isolated in the form of its dihydrochloride, which forms colorless crystals practically insoluble in concentrated hydrochloric acid.

m-Nitroaniline is obtained from dinitrobenzene by taking advantage of the fact that a *single* nitro group can be reduced by sulfides in alkaline solutions. In the laboratory, finely divided *m*-dinitrobenzene is suspended in alcoholic ammonia and hydrogen sulfide is passed in; technically, sodium sulfide or sodium disulfide is used.



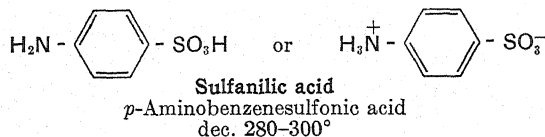
The use of an alkaline sulfide is a *general method* for reducing one only of two or more nitro groups in the same molecule.

PRODUCTS OF ANILINE

Aniline is manufactured in large amounts by the reduction of nitrobenzene and the amination of chlorobenzene (Sec. 13-10). It is almost exclusively an intermediate. Conversions into dimethylaniline, diethylaniline, and acetanilide were described in Chapter 13. Aniline is also the raw material for the manufacture of: phenylglycine, for indigo (Sec. 25-14); various intermediates for azo dyes; and important quantities of rubber-processing chemicals, including the vulcanizing accelerator mercaptobenzothiazole (Sec. 26-12), and antioxidants.

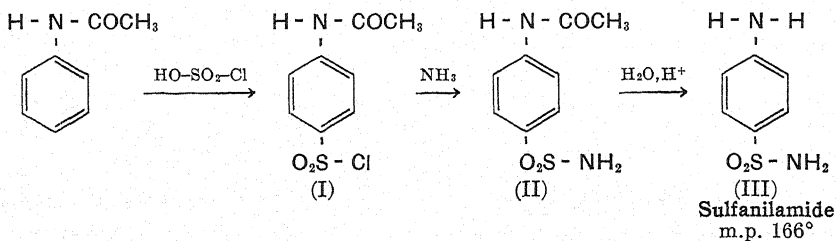
In any study of aniline and its products it should be recalled that the NH_2 group strongly activates the *ortho* and *para* positions and that it also renders the compound readily subject to oxidation with ring cleavage. The usual method of protecting against oxidation, by acetylation, was described in Section 13-15.

23-26 Sulfanilic Acid; Sulfa Drugs. Sulfonation of aniline at 200°C yields

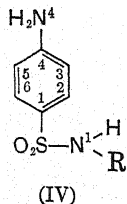


Sulfanilic acid has long been used to some extent as an intermediate for azo dyes (Sec. 25-8). It now has a greater interest as the parent compound of the *sulfa drugs*.

Sulfanilamide, the first drug of this type introduced, is the sulfonamide of sulfanilic acid. It is not manufactured from this acid but from acetanilide, as follows: Acetanilide is sulfonated with chlorosulfonic acid to the sulfonyl chloride (I); this is converted into the amide (II) by the usual reaction with ammonia; the protecting acetyl group is removed by hydrolysis, yielding the desired product (III):

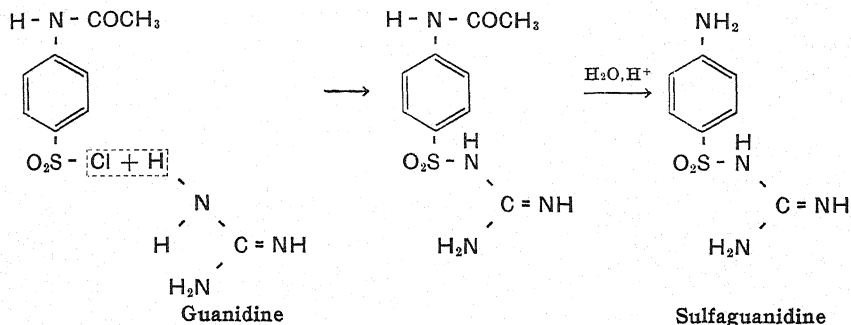


Sulfanilamide was prepared in 1908, but its usefulness as a drug was not suspected until 1935. Something like 4000 related compounds have since been prepared and tested. All the effective ones are of the type in which an N¹ hydrogen atom of sulfanilamide has been replaced by some radical (IV):



Derivatives in which ring hydrogen atoms are substituted show little or no bacteriostatic activity. The same is true of derivatives in which an N⁴ hydrogen is replaced, unless this substituting group can be removed in the body. The general method for preparing the useful derivatives is similar to that just described for sulfanilamide; the difference is that in

the second stage another compound containing the NH_2 group is used instead of ammonia, *e.g.*,



Among the most important of these drugs are three compounds in which the radical R in (IV) is a heterocyclic nucleus (Chap. 26); these are *sulfathiazole*, *sulfapyridine*, and *sulfadiazine*. Sulfa drugs are still produced in large quantities (5 million pounds, USA, 1950), although the more recently discovered antibiotics (Chap. 27) are used for many of the same purposes.

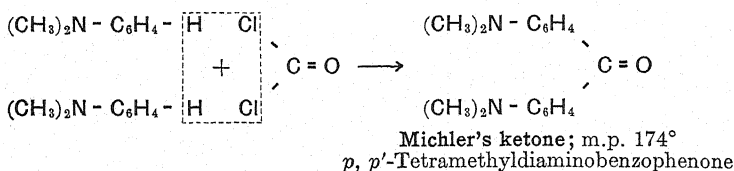
23-27 Bacteriostatic Agents. Diseases due to protozoa were attacked successfully by chemotherapy as early as 1910, when arsphenamine and other organic arsenicals were introduced (Sec. 14-15). Bacterial diseases continued to be fought, as they had been since the time of Pasteur, chiefly by inoculation and immune serum. The sulfa drugs provided the first chemical weapons for use against bacteria within the living body. They have proved highly effective against certain types (*cocci*), including those responsible for streptococcus infections, pneumonias, and gonorrhea.

The action of these drugs is fairly well understood. They do not kill bacteria directly (*i.e.*, are not bactericidal) at the concentrations which are used. Instead, they seem to inhibit the growth or reproduction of bacteria and thus give the natural defenses of the body a better chance. There is considerable evidence that this bacteriostatic action occurs in the following way. Apparently *p*-aminobenzoic acid is a vitamin so far as bacteria are concerned and is required for the normal functioning of some of their vital processes. This compound is not very different, structurally, from the sulfa drugs. It is thought that when a patient receives a large dose of one of the latter, bacteria take it up instead of *p*-aminobenzoic acid. But the substitute cannot perform the necessary function in bacterial metabolism; thus growth and reproduction are inhibited.

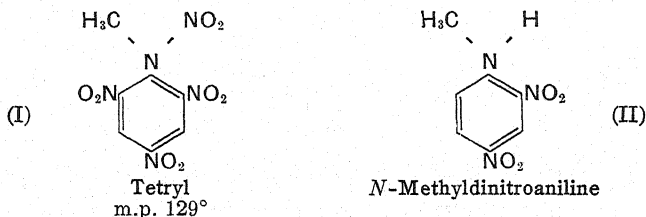
23-28 Dimethylaniline Derivatives. The $\text{N}(\text{CH}_3)_2$ group activates the *ortho* and, especially, the *para* position even more strongly than does

NH₂. It also stabilizes against ready oxidation of the nucleus. Dimethylaniline couples readily in the *para* position with diazonium ions to form azo dyes (Sec. 25·8), condenses with aldehydes (Sec. 25·11), and yields a *p*-nitroso derivative with nitrous acid (Sec. 13·14). Other uses include the manufacture of the following derivatives:

Michler's ketone, an intermediate for triphenylmethane dyes, is produced by reaction between carbonyl chloride and dimethylaniline:



Tetryl, an important military explosive, is made by dissolving dimethylaniline in a large excess of sulfuric acid and treating with mixed acid at about 70°C. A rather involved series of reactions yields the explosive (I):



An alternate method, which is reported to give better yields of a more readily purified product, starts with 1-chloro-2,4-dinitrobenzene. The chlorine atom is replaced by NHCH₃, by reaction with methyl amine in the presence of sodium hydroxide. The product (II) is then dinitrated to tetryl.

Questions

- Write the equations, indicating essential conditions, for the conversion of benzene into: (a) alkylbenzenesulfonates (detergents); (b) BHC; (c) cyclohexane; (d) biphenyl; (e) maleic anhydride.
- (a) Outline with equations the production of styrene from benzene. (b) Predict the direction of addition of HCl and of HOCl to the vinyl radical in styrene monomer. (c) Write a probable formula for styrene trimer.
- Review question 7, Chapter 22.
- (a) Write structural equations for the primary reactions taking place in phenol-formaldehyde condensations. (b) Illustrate how a cross-linked product of high molecular weight can result from repetition of these reactions. (c) If phenol were replaced entirely by a mixture of cresols, how would the thermosetting quality of the product be affected? Explain your reasoning.
- Write structural equations, indicating reagents and necessary conditions for all steps required, in the conversion of *p*-nitrophenol into: (a) the drug acetphenetidin

(Phenacetin), (p -) $C_6H_5O.C_6H_4.NHCOCH_3$; (b) the photographic developer Metol, the sulfate of p -methylaminophenol.

6. Show why p -nitrophenol cannot have a chelated structure.

7. Write structural equations for: (a) the production of salicylic acid from phenol; (b) the conversion of salicylic acid into aspirin and into methyl salicylate.

8. Explain why salicylaldehyde is volatile with steam when its *para* isomer is not.

9. Explain why precautions not required in the nitration of aromatic hydrocarbons become necessary in nitrating phenols.

10. (a) Show how to prepare p -aminophenol from phenol. (b) How should this compound compare with p -nitrophenol with respect to solubility in acids and in alkalis? (c) In view of the use of p -aminophenol as a photographic developer what chemical property is indicated?

11. Explain why resorcinol is the only one of the three isomeric dihydroxybenzenes which can be manufactured by the process of disulfonation and alkali fusion.

12. (a) Discuss the relations and differences between hydroquinone and quinone in terms of structure and properties. (b) Explain why no *meta* quinone can be expected.

13. (a) Give typical reactions of phloroglucinol which force the conclusion that it is a tautomeric substance. (b) Show how it is possible to represent phenol by two "ketonic" formulas somewhat analogous to that of phloroglucinol.

14. Write structural equations for the preparation of: (a) *o*-anisidine from chlorobenzene and from phenol; (b) guaiacol from *o*-anisidine; (c) vanillin from guaiacol by the Reimer-Tiemann reaction; (d) *o*-dianisidine (see formula, Sec. 25-8) from *o*-nitrophenol.

15. (a) Write the equations for two examples of nitrosation. (b) Explain why nitrosobenzene cannot be obtained in similar fashion. (c) Why does not aniline yield a p -nitroso compound?

16. (a) Show how aniline sulfate and sulfanilic acid differ in structure. (b) The amino acids described in Chapter 21 form salts both with bases and with acids. Explain why sulfanilic acid forms salts only with bases.

17. (a) Explain why the manufacture of sulfa drugs always starts with acetanilide rather than with sulfanilic acid. (b) Given acetanilide and 2-aminopyridine (Sec. 26-1) write the equations for the preparation of sulapyridine.

18. (a) Write full structural equations for all reactions involved in the conversion of aniline into p -nitroaniline. Explain the necessity for *protection* by acylation. (b) Show how p -nitroaniline can be made from chlorobenzene. (c) Explain why it is not made by the method used for *m*-nitroaniline.

19. (a) Outline a method, based on differential solubility, for separating *m*-nitroaniline from *m*-dinitrobenzene. (b) Write the structural formulas of *m*-diaminobenzene (*m*-phenylenediamine) and diphenylamine. How would these substances differ, if at all, in their reactions with nitrous acid? (c) *m*-Phenylenediamine is freely soluble in water and is commonly isolated as its sparingly soluble dihydrochloride. Write the full structural formula for the latter compound.

20. What reagents are used when it is desired to reduce: (a) nitrobenzene to aniline and to hydrazobenzene; (b) *m*-dinitrobenzene to *m*-phenylenediamine; (c) *m*-dinitrobenzene to *m*-nitroaniline?

21. (a) Write equations for the series of reactions by which *m*-aminophenol can be made from nitrobenzene. (b) How could *m*-aminophenol be converted into resorcinol?

22. Prepare a chart similar to Figure 23-2 indicating the necessary reactions through which aniline is converted into the following compounds: acetanilide; acetyl-

p-phenylenediamine; dimethylaniline; diphenylamine; hydroquinone; Michler's ketone; *p*-nitroacetanilide; *p*-nitroaniline; *p*-nitrosodimethylaniline; *p*-phenylenediamine; quinone; sulfanilamide; sulfanilic acid; tetryl.

23. Referring to Figures 23-1 and 23-2, check your ability to write equations and specify essential conditions for all the chemical conversions indicated by the arrows. (Omit at this time, but include in your final review, the few reactions not yet studied, *e.g.*, the formation of azo dyes by coupling and those involving phthalic anhydride.)

CHAPTER 24

POLYFUNCTIONAL AROMATIC COMPOUNDS

III. PRODUCTS OF TOLUENE AND NAPHTHALENE

Toluene is obtained as a by-product of coking and in greater quantity by the chemical conversion of petroleum hydrocarbons (Sec. 6·18). It is a valuable industrial solvent and a desirable antiknock component of motor fuel. Like benzene it is converted through chemical reactions into valuable intermediates and finished products. Most of these result from reaction series which begin with *nitration*, *chlorination*, or *sulfonation*.

24·1 Nitration of Toluene. The activating and directing influence of the methyl side chain is shown in the mononitration of toluene. This proceeds fourteen times as fast as with benzene under the same conditions and yields a mixture of *o*-nitrotoluene and *p*-nitrotoluene with only about 4 per cent of the *meta* isomer. Reaction can be stopped readily at this stage and the major products isolated and purified. On reduction they yield *o*- and *p*-toluidine, which are intermediates for azo dyes. *p*-Nitrotoluene is used also for the production of *p*-aminobenzoic acid by the series of reactions outlined in Figure 22·2. This acid yields esters which are important local anesthetics, notably procaine (Sec. 26·16).

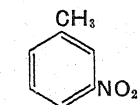
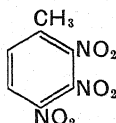
On dinitration, both *o*- and *p*-nitrotoluene yield 2,4-dinitrotoluene, which gives derivatives analogous to those obtainable from dinitrobenzene.

24·2 TNT, 2,4,6-trinitrotoluene, is manufactured by nitrating toluene in two stages (formerly three), with increasing temperatures and concentration of mixed acid. These more drastic conditions are necessary because each deactivating nitro group introduced makes further substitution more difficult.¹ The solidified crude product consists of crystals of almost pure 2,4,6-trinitrotoluene (α -TNT) coated with about 4 per cent of oily isomers. After purification, TNT (m.p. 80.7°C) is loaded into shells by pouring in the liquid state and sets on cooling to a hard crystalline mass.

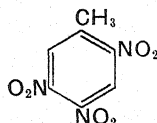
¹ It is interesting to note that the activating effect of the methyl group is not entirely suppressed by the nitro groups in 2,4-dinitrotoluene; this compound is further nitrated on a large scale, while the corresponding nitration of 1,3-dinitrobenzene is too difficult for practical application. TNB (1,3,5-trinitrobenzene), a valuable explosive for certain special purposes, is made on a small scale from TNT. Oxidation of the methyl side chain by dichromic acid gives 2,4,6-trinitrobenzoic acid. The latter is decarboxylated to TNB with exceptional ease; suspending in boiling water suffices to eliminate CO₂.

TNT was the most important military high explosive in the First and Second World Wars. It was used as the bursting charge in shells, mines, and torpedoes and for the demolition of bridges, etc. Like nitroglycerin and dynamite it is a brisant explosive but, unlike these substances, it is not easily detonated. TNT is stable toward shocks received in handling and, what is of primary importance, is unaffected by the explosion of the propellant which sets a shell in motion. It is known that a rifle bullet can be fired through a block of TNT without effect. The explosion of a shell is initiated by a small amount of a *detonator*, e.g., lead azide or mercury fulminate, in its fuze. This ignites a slow-burning train of black powder which in turn sets off a larger charge of an intermediate explosive such as tetryl (the *booster*). The shock of this explosion is sufficient—and necessary—to start the decomposition of the bursting charge. The latter is often Amatol, a mixture of TNT and ammonium nitrate.

Purification of TNT. The oily isomers which coat the crystals of crude TNT result from the formation of about 4 per cent of *m*-nitrotoluene in the mononitration. During further nitration this is converted into unsymmetrical isomers of α -TNT, mainly 2,3,4- and 2,4,5-trinitrotoluene.

*m*-Nitrotoluene

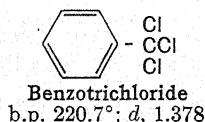
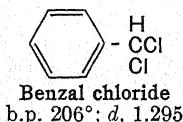
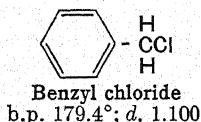
2,3,4-Trinitrotoluene



2,4,5-Trinitrotoluene

These isomers are dissolved out by agitating the crude crystals with a solution of sodium sulfite. The action of this reagent depends upon an interesting mutual influence of nitro groups which, when situated *ortho* to one another, cooperate to place an exceptionally high positive charge on the carbon atoms to which they are joined. Thus one of these atoms is readily attacked by the nucleophilic sulfite ion and NO_2 is displaced by SO_3Na . The resulting sulfonate readily dissolves in water (giving a deep red solution) and can be washed away from the insoluble and unreacted α -TNT.

24.3 Products of Chlorination. The general conditions necessary for the side-chain chlorination of toluene were described in Section 5-15. Usually the passage of chlorine is continued until the density of a sample shows that the mixed product consists mainly of benzal chloride:



Unchanged toluene (b.p. 110.6°C) and benzyl chloride are readily removed and separated from each other by fractional distillation. The

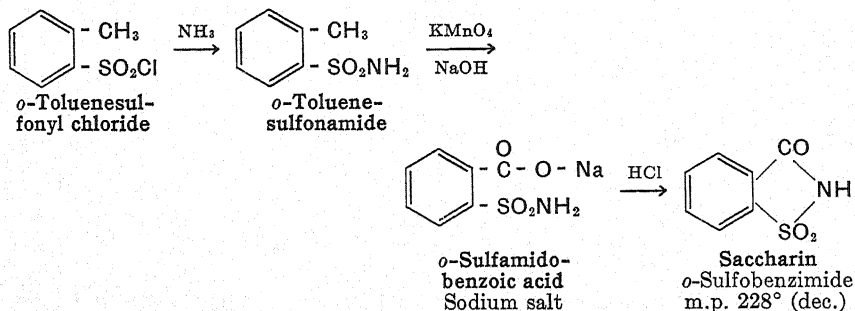
residual mixture of benzal chloride and benzotrichloride is hydrolyzed, by heating with milk of lime, to benzaldehyde and calcium benzoate. Benzaldehyde is distilled off with steam and may be further purified through its bisulfite addition compound. This is the major industrial source of benzaldehyde (cf. Sec. 10-17) and its products, which include cinnamic acid and its esters, malachite green, benzyl benzoate,¹ etc.

The by-product benzoic acid from this process is always contaminated with chlorobenzoic acids formed through nuclear substitution in the later stages of chlorination. These are objectionable for most purposes and are hard to remove. Most benzoic acid is now manufactured by the decarboxylation of phthalic anhydride (Sec. 24-10).

The side-chain chlorination of toluene is often controlled so that the chief product will be benzyl chloride. The latter is widely used (cf. Sec. 7-21) for introducing the benzyl radical into other organic compounds. It is also the starting point for the manufacture of phenylacetic acid, phenylethyl alcohol, and their many esters used in the synthetic-perfumes industry.

24-4 Products of Sulfonation. When toluene is sulfonated at 100°C with sulfuric acid, about 85 per cent of the product is *p*-toluenesulfonic acid. A better yield of the *ortho* isomer can be obtained by treating cold toluene with a large excess of chlorosulfonic acid (Sec. 14-4). This yields the *ortho* and *para* sulfonyl chlorides in the proportion of about 40 to 60, and these can be separated by fractional crystallization. The *ortho* compound is used in the manufacture of saccharin and the sulfone-phthalein indicators (Sec. 25-27). The *para* compound yields the chloramine antiseptics.

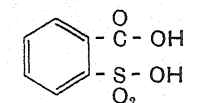
Saccharin is made by the following series of reactions:



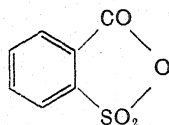
Saccharin is about 500 times as sweet as cane sugar and is sometimes used

¹ Benzyl benzoate (Benylate) is made from benzaldehyde by the Cannizzaro reaction, followed by the esterification reaction between benzyl alcohol and benzoic acid. It is used in ointments against skin infections (scabies or "itch") and in military delousing sprays.

as a substitute in sweetening food products and by diabetics. It has no food value. Saccharin is the cyclic imide of *o*-sulfobenzoic acid. Both this acid and its cyclic anhydride are known:

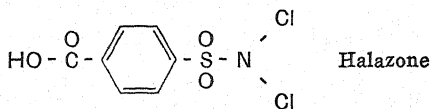


o-Sulfobenzoic acid



o-Sulfobenzoic anhydride

Halazone. Sulfonamides (Sec. 14.5) react with alkaline solutions of sodium hypochlorite to yield products in which the hydrogen atoms of the NH_2 group are replaced by chlorine atoms. Such *N*-halides react readily with water to liberate free chlorine, which is destructive to most microorganisms. Tablets containing halazone are used, especially by



Halazone

troops in the field, for sterilizing drinking water. The tablets also contain enough sodium carbonate to impart water solubility by forming the sodium salt of this carboxylic acid.

PRODUCTS OF NAPHTHALENE

24.5 The compounds manufactured from naphthalene are divided conveniently, on the basis of chemical structure, into the following classes:

Substitution products are compounds of the same nuclear structure as *naphthalene*, made from it by replacing one or more hydrogen atoms.

Phthalic anhydride and its derivatives. The largest single use of naphthalene is oxidation to phthalic anhydride. In this reaction, one ring is opened and two carbon atoms are oxidized away. Hence, phthalic anhydride and its derivatives contain the *benzene* instead of the *naphthalene* nucleus.

Anthraquinone and its derivatives. An important use of phthalic anhydride is in condensations leading to anthraquinone and substituted anthraquinones. Structurally, these compounds are *anthracene* derivatives.

Addition Products. Hydrogen is added to the naphthalene nucleus by various reagents which do not affect benzene, and it is possible to obtain products in which two, four, six, eight, or ten hydrogen atoms have combined. By catalytic hydrogenation above 100°C , four and then six hydrogen atoms are added in two stages, saturating one and then both

rings. The products are tetrahydronaphthalene, $C_{10}H_{12}$ (Tetralin), and decahydronaphthalene, $C_{10}H_{18}$ (Decalin). Both are useful solvents.

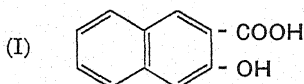
24-6 Naphthalene Substitution Products. Naphthalene yields many substitution products that are valuable intermediates for the manufacture of azo dyes. Aside from α -naphthol and β -naphthol and the corresponding naphthylamines, these are mostly monosulfonic or disulfonic acids containing either an OH or NH_2 group or both. Some of those produced in largest amounts are shown in Table 24-1.

TABLE 24-1 POLYSUBSTITUTED NAPHTHALENE INTERMEDIATES

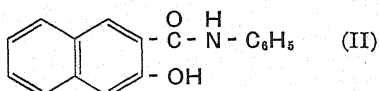
Systematic Names	Trivial Names
2-Amino-1-naphthalenesulfonic acid.....	Tobias acid
4-Amino-1-naphthalenesulfonic acid.....	Naphthionic acid
8-Amino-1-naphthalenesulfonic acid.....	Peri acid
8-Amino-1-naphthol-3,6-disulfonic acid....	H acid
7-Amino-1-naphthol-3-sulfonic acid.....	Gamma acid
3-Hydroxy-2-naphthoic acid.....	(See Naphthol AS)
2-Naphthol-3,6-disulfonic acid.....	R acid
2-Naphthol-6,8-disulfonic acid.....	G acid
1-Naphthol-4-sulfonic acid.....	Neville and Winther's acid
2-Naphthol-6-sulfonic acid.....	Schäffer's acid

The long systematic names are usually replaced in industry by short ones which are more convenient but nondescriptive. Explanatory lists may be found in the ordinary handbooks of chemistry.

Naphthol AS Compounds. The naphthalene carboxylic acids are called naphthoic acids. 3-Hydroxy-2-naphthoic acid (I) is manufactured from β -naphthol by the Kolbe reaction. It condenses with aniline in the presence of phosphorus trichloride to yield its anilide (II), usually known in the dyestuffs industry as naphthol AS. (The letters AS are derived from its German name ending in *anilid saure*.)



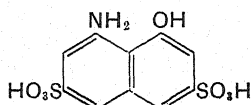
3-Hydroxy-2-naphthoic acid



Naphthol AS

Various related compounds are manufactured by substituting other aryl amines for aniline (*e.g.*, *o*-toluidine gives naphthol AS-D). This group of compounds has special importance for the production of azoic dyestuffs (Sec. 25-21).

24-7 Methods of Production. Most of the important naphthalene substitution products are obtained through the use of four general reactions, *sulfonation*, *alkali fusion*, *nitration*, and *reduction*. These are supplemented by the Bucherer reaction (Sec. 24.8). The exact conditions are varied according to experience in order to obtain the best yields of the desired products. The manufacture of H acid

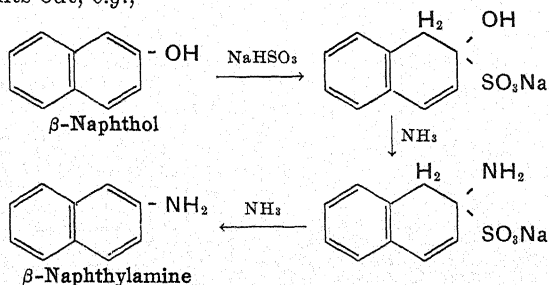


H acid
8-Amino-1-naphthol-3,6-disulfonic acid

involves a typical sequence of general reactions: Naphthalene is sulfonated under conditions which yield principally the 1,3,6-trisulfonic acid; nitration followed by reduction places the NH_2 group at position 8; a carefully regulated alkali fusion introduces OH in place of the SO_3H at position 1.

Directing influences in monosubstitution were referred to in Section 5-24, where it was pointed out that nitration and halogenation occur only in the *alpha* positions and that the results of sulfonation depend largely upon temperature. When a second group substitutes, its position is influenced also by the nature and position of the first. Without going into details, it suffices to point out that the rule of *alpha* substitution in nitration still holds good and that, nearly always, any second group becomes attached to the unsubstituted ring. Control of the temperature at which naphthalene is sulfonated makes possible a good yield of either 1- or 2-naphthalenesulfonic acid (Sec. 14-3). Alkali fusion of the sulfonates yields α - and β -naphthol, respectively; the latter is much the more important.

24.8 Bucherer Reaction. Since nitration occurs only in the *alpha* positions (1, 4, 5, 8), these are the only ones in which it is possible to introduce an NH_2 group by the usual procedure of nitration and reduction. For the manufacture of β -naphthylamine and other compounds with an amino group at 2, 3, 6, or 7, the Bucherer reaction is used. This consists in heating a naphthol (preferably under pressure) with sodium bisulfite and ammonia. Bisulfite adds to a keto form of the naphthol (cf. Sec. 23-22), OH in the addition product is replaced by NH_2 , and NaHSO_3 splits out, *e.g.*,

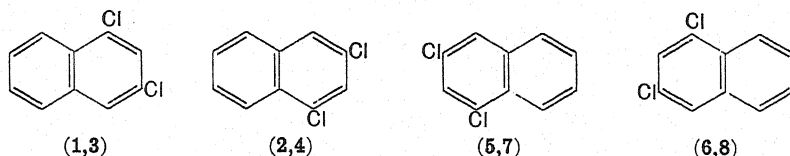


These reactions are all reversible, and the Bucherer method is used frequently in the naphthalene series to replace NH_2 by OH; *e.g.*, 1-naphthylamine-4-sulfonic acid is converted into 1-naphthol-4-sulfonic acid by heating with a solution of bisulfite and then with sodium hydroxide. The

Bucherer reaction is seldom of value in the benzene series (where monohydric phenols have much less tendency toward ketonization).

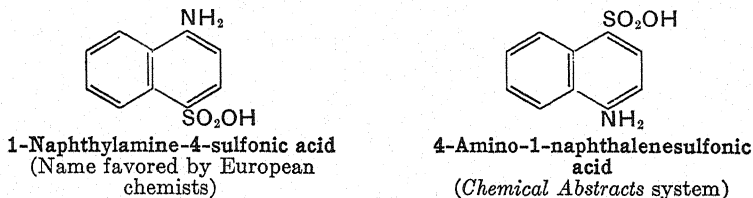
24-9 Isomerism and Nomenclature. The fact that monosubstitution products of naphthalene can be obtained in two isomeric forms, α and β , has already been noted. When two hydrogen atoms are replaced by identical groups, 10 isomeric disubstitution products are possible; for example, 10 dichloronaphthalenes, $C_{10}H_8Cl_2$, are known. The number of possibilities is still larger when the substituents are unlike and when three or more hydrogen atoms are replaced. While all these possibilities have not been realized, the number of polysubstitution products known and in common use is large. In order to avoid confusion, careful attention to nomenclature is necessary.

Nomenclature. The prefixes α and β are used only for monosubstitution products; when two hydrogen atoms have been replaced, positions are always indicated by the numbers of the carbon atoms to which they are attached. (The terms *ortho*, *meta*, and *para* are never used in connection with naphthalene derivatives.) Even with this system, ambiguity is possible. For example, each of the following formulas represents the same compound:



This source of confusion is avoided by the rule that the *sum* of the numbers shall be the smallest possible. Accordingly, the first of the above formulas is used and the compound is called 1,3-dichloronaphthalene.

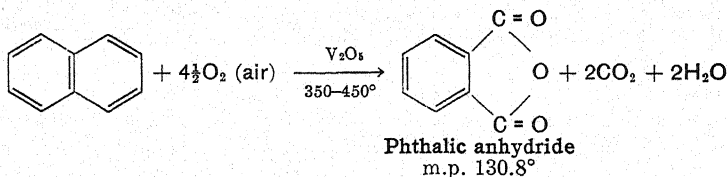
With unlike substituents, different names arise for the same substance, depending on which is chosen to start the numbering. For example, the same compound is represented and described by both of the following formulas and names:



In practice, this compound is ordinarily called *naphthionic acid*.

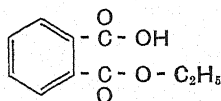
PHTHALIC ANHYDRIDE AND ITS PRODUCTS

24-10 Phthalic anhydride (the anhydride of *o*-benzenedicarboxylic acid) is manufactured by the catalytic oxidation of naphthalene vapors:

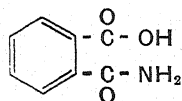


The contact time is only about 0.1 second but, even so, some molecules are further oxidized by opening of the second ring and maleic anhydride is a by-product. Phthalic anhydride is also manufactured in similar fashion by the catalytic oxidation of *o*-xylene.¹ Current production (1951) of phthalic anhydride in the United States exceeds 200 million pounds a year and is increasing rapidly. Its largest uses are for the manufacture of alkyd resins, phthalate plasticizers, and anthraquinone, as described below. Minor uses include conversion to phthalimide and anthranilic acid and the manufacture of phenolphthalein and of xanthene dyes. Phthalic anhydride is now the major industrial source of *benzoic acid*. The latter is obtained in 85 per cent yield when phthalic anhydride is decarboxylated by heating with steam at 200°C in the presence of a catalyst consisting of sodium and chromium phthalates.

24.11 Phthalates; Plasticizers. Phthalic anhydride reacts like acetic anhydride, though more slowly, with alcohols, ammonia, amines, etc. Only one molecule of the other substance is involved in the reaction which opens the anhydride ring; hence, the initial product always contains one COOH group, *e.g.*,



Ethyl hydrogen
phthalate



Phthalamic acid

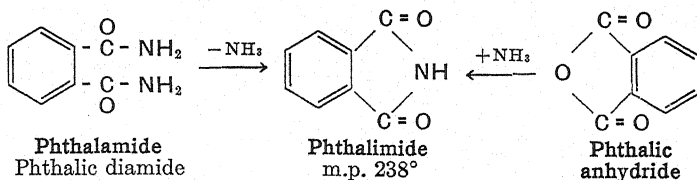
This group in the monoalkyl esters can be esterified in the usual way, by boiling with excess of the alcohol and catalytic amounts of mineral acid. Large quantities of dialkyl phthalates are manufactured, for use mainly as plasticizers, *e.g.*, dibutyl phthalate, b.p. 340°C. The one produced and used in largest amounts is a dioctyl phthalate (often referred to as DOP) obtained by reaction between phthalic anhydride and 2-ethylhexanol. This di-2-ethylhexyl phthalate is a very viscous liquid with a vapor pressure of only about 0.1 mm at 150°C.

Plasticizers are high-boiling (essentially nonvolatile) organic compounds which are admixed with many synthetic resins to improve some

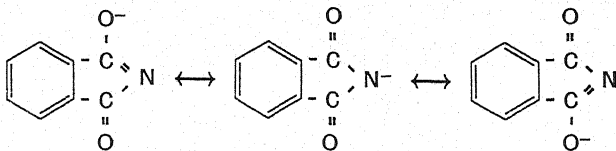
¹ The side-chain oxidation of xylenes is rapidly becoming an important industrial reaction since large amounts became available by synthesis from petroleum (Sec. 6-18). The chief difficulty is the separation of the three isomers, all of which boil within a narrow range. *p*-Xylene is oxidized to terephthalic acid (*p*-benzenedicarboxylic acid) and *m*-xylene yields isophthalic acid. Neither of these acids forms a cyclic anhydride. Terephthalic acid condensed with ethylene glycol yields the polyester fiber, Dacron or Terylene. It is expected that isophthalic acid will replace phthalic anhydride for certain purposes.

physical property; this may be, for example, to increase the ease of molding or shaping, or to impart elasticity to a lacquer film. The dialkyl phthalates constitute the most important class. Others include phenolic esters of phosphoric acid (triphenyl and tricresyl phosphates) and various esters of oleic and stearic acids. Most plasticizers are liquids, but camphor, which is used in certain resinous products, is a soft solid.

24.12 Phthalimide is formed by heating the diamide of phthalic acid but is most conveniently obtained by passing ammonia gas over heated phthalic anhydride:

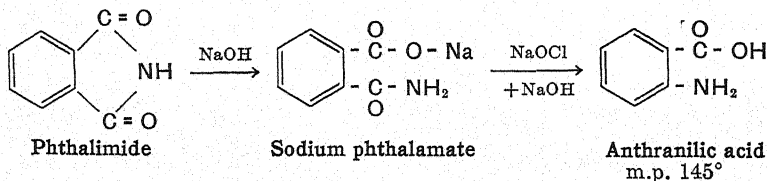


Phthalimide is insoluble in water but dissolves in alkalis, thus showing that it has acidic properties. The *N*-hydrogen atom is ionized to an extent somewhat greater than the OH hydrogen of phenol, and the compound therefore forms sodium and potassium salts. This fact is ascribed to stabilization of the resulting anion by resonance among the three forms:



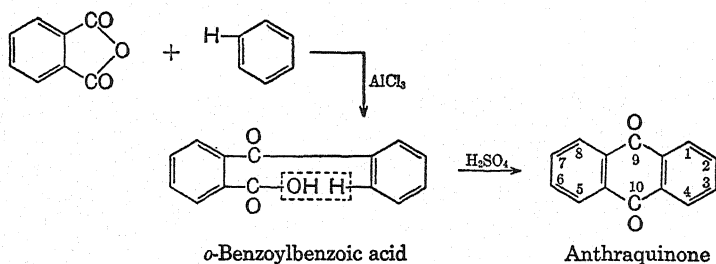
Potassium phthalimide is used in the laboratory preparation of primary alkyl amines and amino acids (Gabriel synthesis), as was illustrated in Section 21.2.

Anthranilic acid (*o*-aminobenzoic acid) is best obtained from phthalimide by the Hofmann reaction (Sec. 12.15):



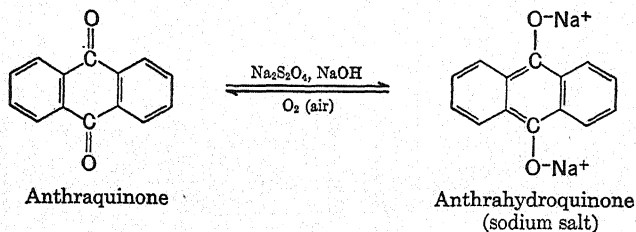
Methyl anthranilate and other esters, *e.g.*, ethyl and phenylethyl, are used in the perfume industry. Anthranilic acid itself is used in making a few azo dyes; formerly, it was an important intermediate for indigo.

24.13 Anthraquinone, $C_{14}H_8O_2$, is manufactured from phthalic anhydride and benzene. These condense in the presence of anhydrous aluminum chloride to give *o*-benzoylbenzoic acid. When the latter is heated with sulfuric acid, water is eliminated with ring closure, yielding anthraquinone:



Phthalic anhydride condenses in like manner with toluene, chlorobenzene, *p*-chlorophenol, and similar compounds; these reactions lead to methylanthraquinone, chloroanthraquinone, and many other important derivatives. By using substituted phthalic anhydrides it is possible to obtain in like manner derivatives of anthraquinone with substituents in the 5, 6, 7, or 8 positions. The one significant use of anthraquinone and its substitution products is for the manufacture of dyestuffs, mainly vat dyes (Sec. 25.15).

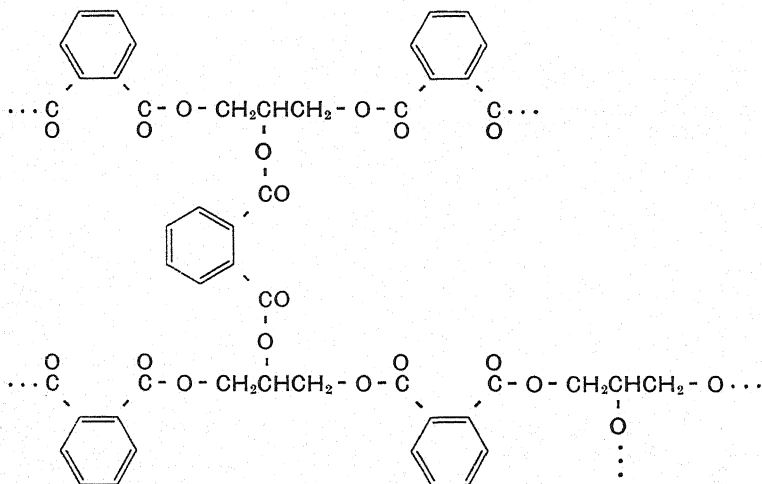
Anthraquinone crystallizes in odorless, faintly yellow needles or prisms (m.p. $285^\circ C$; b.p. $379.8^\circ C$). It is not volatile with steam but can be sublimed without decomposition. It is insoluble in water and only sparingly soluble in most organic liquids; it dissolves in warm concentrated sulfuric acid and separates unchanged on dilution. Anthraquinone is not affected by sulfurous acid (cf. Sec. 23.20) but is converted by stronger reducing agents, such as an alkaline solution of sodium hydrosulfite, $Na_2S_2O_4$, into a deep red solution of anthrahydroquinone. The latter is oxidized back to anthraquinone on exposure to air:



The analogous reactions of anthraquinone derivatives are utilized in vat dyeing (Sec. 25.23).

24-14 Alkyd¹ resins are thermosetting condensation polymers formed by esterifying polyhydric alcohols with polybasic acids or their anhydrides. Glycerol and phthalic anhydride are the materials used in largest amounts. They react by esterification around 160 to 170°C to form a resinous product which is fluid at that temperature and is soluble in suitable organic liquids. On more prolonged heating, viscosity increases until gelation occurs suddenly. This product, when cooled, is hard and brittle and no longer soluble or fusible. In the manufacture of alkyd resins, heating is interrupted in time to obtain a product which is still plastic and soluble. The major use is in surface coatings; a solution is sprayed or brushed upon an object, which is then heated to convert the resin into the insoluble form and give a tough, adherent protective finish. Or an article such as a coil winding for an electric motor may be dipped and then baked to produce a thin but rugged, waterproof coating.

Alkyds in the soluble stage consist mainly of linear esters. During the thermosetting or *curing* stage, further reactions occur between COOH and OH groups of different chains, thus producing cross-linked, three-dimensional structures (cf. Bakelite, Sec. 23-8). A very small portion of such a cross-linked alkyd may be indicated as follows:



Alkyd resins made exclusively from glycerol and phthalic anhydride have limited usefulness for certain purposes and are commonly modified in various ways; *e.g.*, these components may be replaced in part by pentaerythritol and maleic anhydride, respectively. Sometimes the

¹ The name alkyd combines sounds from the words *alcohol* and *acid*. The trade name Glyptal, applied to the products of one manufacturer, is a condensation of *glycerol-phthalic*.

number of possible cross linkages is reduced by including in the reaction mixture a long-chain fat acid (or a resin acid) or by using a monoglyceryl ester of such an acid for part of the glycerol. The most important modification consists in including a drying oil (*e.g.*, linseed, soybean) and a suitable drier (Sec. 16·24). These oils dry faster than normally when incorporated in the alkyd plastic, and tough and durable films can be obtained *either* by atmospheric oxidation or by baking. This is the type of modified alkyd resin now used so widely as protective coatings on automobiles, busses, bridges, and innumerable articles of household, farm, and military equipment.

24·15 Plastics Industry. The manufacture of synthetic resins and plastics has grown steadily in the United States since the introduction of Bakelite in 1907. It is now a major industry, with a total production in excess of any metal other than iron, and continues to expand rapidly. Thus it calls for an ever-increasing supply of its basic organic raw materials—phenol, formaldehyde, styrene, phthalic anhydride, glycerol, vinyl compounds, urea, etc. The relative amounts of the more important classes, with their largest single fields of application, are given in Table 24·2.

TABLE 24·2 PRODUCTION OF SYNTHETIC RESINS AND PLASTICS; USA, 1950†
Millions of Pounds

Phenolic and other tar-acid resins.....	451
Molding materials, 50 per cent	
Styrene polymer and copolymer resins.....	355
Molding materials, 75 per cent	
Vinyl and vinyl copolymer resins.....	426
Sheeting and film, 53 per cent	
Alkyd resins.....	402
Protective coatings, 100 per cent	
Urea and melamine resins.....	219
Adhesive resins, 40 per cent	
Coumarone-indene and petroleum polymer resins.....	143
Rosin modifications (protective coatings).....	74
Miscellaneous‡.....	125
Total (approximately).....	2,200

† These figures (US Tariff Commission, *Preliminary Report for 1950*) omit plastic materials derived from natural, cellulosic materials (cellophane, cellulose nitrate, cellulose acetate, etc.). The production of cellulose acetate plastics was around 110 million pounds.

‡ Includes polyethylene, acrylic materials, nylon, silicones, etc.

Questions

1. (a) Show how the usual directing influences cooperate to yield α -TNT as the principal product of the trinitration of toluene. (b) Explain accurately the origin of a small amount of the unsymmetrical isomers and the effects which make it possible to remove them by the action of sodium sulfite.

2. Outline the necessary experimental conditions for the laboratory preparation

of *p*-bromobenzyl chloride and show what product this compound would give on oxidation.

3. Write full structural equations for all the reactions necessary in the preparation of the following compounds from benzaldehyde (use of ethyl alcohol permitted): (a) ethyl phenylacetate; (b) ethyl cinnamate; (c) benzoyl chloride; (d) mandelic acid, $C_6H_5.CH(OH).COOH$.

4. Write full structural equations for the reactions involved in making the following compounds from toluene: (a) *o*-nitrobenzoic acid (through *o*-nitrotoluene); (b) *o*-chlorobenzoic acid (through *o*-nitrotoluene); (c) acetyl-*p*-toluidine; (d) *m*-aminobenzoic acid; (e) *p*-aminobenzoic acid; (f) *m*-hydroxybenzoic acid; (g) *m*-hydroxybenzaldehyde; (h) 2-nitro-*p*-toluidine ($NH_2 = 1$); (i) 4-amino-*m*-toluenesulfonic acid.

5. Show that saccharin and *o*-sulfobenzoic anhydride are related in the same way as phthalimide and phthalic anhydride.

6. (a) Write the structural formulas and give the correct names of the 10 possible dichloronaphthalenes, $C_{10}H_8Cl_2$. (b) Prove that there are theoretically possible more naphthalene substitution products of the composition $C_{10}H_8ClBr$ than there are dichloronaphthalenes.

7. The product obtained by the mononitration of 1,3,6-naphthalene-trisulfonic acid is usually called "1-nitronaphthalene-3,6,8-trisulfonic acid." Show that this name is justified and does not imply any change in the positions of the SO_3OH groups.

8. Write full structural equations for all the reactions involved in the production of the following compounds from naphthalene: (a) α -naphthol; (b) β -naphthol; (c) α -naphthylamine; (d) β -naphthylamine; (e) decalin; (f) phthalic anhydride; (g) naphthol AS.

9. (a) Write the formula of the product formed when phthalic anhydride is dissolved in an excess of cold concentrated ammonia. (b) What product is formed when the above solution is acidified with cold dilute acid? (c) Explain how the monoalkyl and dialkyl esters of phthalic acid are made.

10. (a) Give an explanation based on space considerations for the fact that isophthalic (1,3-benzenedicarboxylic) acid yields no anhydride. (b) Write equations for the series of reactions by which this acid can be made in the laboratory from benzoic acid. (c) How is terephthalic acid (1,4-benzenedicarboxylic acid) made from *p*-xylene? (d) Show the essential structure of the polyester, Dacron, which it forms with ethylene glycol.

11. Anthranilic acid can be made in the laboratory by acetylating *o*-toluidine, oxidizing the methyl group by permanganate, and hydrolyzing the product. (a) Write equations for these reactions and explain the reason for acetylation. (b) In the final precipitation of the product, the solution is made *faintly* acidic. Explain why solubility is increased by too much HCl or H_2SO_4 .

12. (a) Write full structural equations for the condensation of phthalic anhydride with chlorobenzene to form a derivative of anthraquinone. (b) Show the structural changes involved when anthraquinone is reduced by sodium hydrosulfite.

13. Show that an ester condensation between phthalic anhydride and polyethylene glycol can yield only a linear polymer.

14. Show by structural equations how cross-linked, thermosetting resins can be made: (a) by the condensation of maleic acid with pentaerythritol; (b) by the condensation of resorcinol with formaldehyde; (c) by the condensation of urea with formaldehyde (through dimethylolurea, Sec. 19-11).

15. A mixture of phthalic anhydride, glycerol, and oleic acid is heated to produce a modified alkyd resin. Show clearly why, when this resin is cured by further heating, the number of cross linkages formed would be influenced by the amount of oleic acid used.

CHAPTER 25

COLOR AND CONSTITUTION; DYES AND DYEING

Most pure organic compounds are *colorless*. This includes the great majority of the "intermediates" described in the last two chapters. But, by further chemical changes, these colorless intermediates can be and are converted into intensely colored products. Many of the latter have also the other properties that make them useful as dyestuffs or as biological stains or indicators.

Like all physical and chemical properties of organic compounds, color is intimately related to molecular structure. These relations have been studied intensively, partly because they have practical applications in the dyestuffs industry, and partly because the findings contribute to our knowledge of the effects of molecular structure upon properties in general.

We know much more about the connection between chemical structure and color than about structure and odor—and vastly more than we know about the effects of structure on the activity of drugs. One important reason for the difference is that we do not have to rely solely upon the subjective color sensations received through the eye. Instead, instruments have been developed—the spectroscope and the spectrophotometer—which make it possible to measure color objectively and to express the results quantitatively.

THE ORIGIN OF COLOR

25.1 Light. Electromagnetic radiation includes, in the order of increasing wave length: cosmic rays, gamma rays, X rays, ultraviolet rays, visible *light*, infrared (heat) rays, and the electrical waves used in radio transmission. All these are identical in their fundamental nature, and all move with exactly the same velocity, 3×10^{10} cm per second. They differ in wave length, in frequency, and in energy.

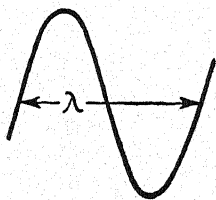


Fig. 25.1

Regarding radiation as a wave motion, its *wave length*, λ , is the straight-line distance between corresponding points on the curve of Figure 25.1, or the distance the wave advances while completing one cycle. Wave

length is usually expressed in angstroms. By *light*, we refer to that band of radiation to which the human eye is sensitive—that is, from about 4000 Å (violet) to about 7600 Å (red). When received collectively by the eye the radiation of this band produces the sensation described as whiteness or absence of color. But if this same “white” light (e.g., ordinary sunlight) is refracted by passing through water drops in the sky, or through the triangular prism of a spectroscope, waves of different lengths are spread out and reach the retina at different points. Each then produces a color sensation peculiar to its wave length, and we see the *spectrum* of white light, as exemplified by the rainbow. The colors are violet, indigo, blue, green, yellow, orange, and red, in the order of increasing wave length.

The *frequency* of radiation is the number of waves passing a point *per second*. It is calculated by dividing the speed of radiation (3×10^{10} cm per second) by the wave length in centimeters. Since the speed is constant, it follows that *the shorter the wave length, the higher the frequency*. For example the frequency of a red ray of wave length 7500 Å ($= 7.5 \times 10^{-5}$ cm) is 4×10^{14} waves per second (3×10^{10} cm $\div 7.5 \times 10^{-5}$ cm $= 4 \times 10^{14}$); a 4000 Å violet ray must complete 7.5×10^{14} , or nearly twice as many cycles in order to advance the same distance in the same time. Ultra-violet rays (2000 to 4000 Å) have still higher frequencies.

25-2 Color and Selective Absorption. Most substances which are colored owe this property to their *selective* absorption of light rays. That is, when illuminated by white light, they stop waves of certain frequencies and reflect or transmit the others. The combined effect on the retina of all the waves reflected or transmitted produces the color sensation experienced—yellow, blue, red, or whatever it may be. In the simplest cases, selective absorption is confined to one or two rather narrow bands of waves. These *absorption bands* can be seen and their positions in the spectrum noted by looking into the eyepiece of a spectroscope when a dilute solution of a suitable colored substance is placed between the slit of the instrument and a source of white light. For example, a very dilute solution of the dyestuff methylene blue shows two narrow absorption bands in the red while the remainder of the red and *all the other* spectral colors are transmitted; the blue color of such a solution, as viewed by the naked eye in daylight, is the combined effect of all the rays from the sun *minus* the particular red ones absorbed.

Similar absorption bands in the *ultraviolet*, exhibited by many *colorless* compounds, can be located by focusing the eyepiece of the spectroscope on a photographic plate. Some colorless substances, absorbing only in the ultraviolet, give derivatives that are colored because they absorb waves of longer wave length corresponding to the visible spectrum. In

like manner, a greenish-yellow substance which absorbs violet rays at around 4100 Å may be given a deeper color by introducing groups which shift its absorption band in the direction of the longer rays; thus if the absorption can be moved over into the region of blue-green rays, around 4900 Å, the object will appear red to the naked eye. The color observed is the complement of the color absorbed. In general, as the region of absorption moves away from the violet (short wave) toward the red (long wave) end of the spectrum, the *observed* color changes in the order: yellow, orange, red, violet, indigo, blue, green. This is the order which scientists describe as *increasing depth*¹ of color (Table 25-1).

TABLE 25-1 RELATION BETWEEN LIGHT ABSORBED AND VISIBLE COLOR

Region of absorption, Å		Color of waves absorbed	Visible color of the object absorbing
↑ Increasing frequency of the radiation absorbed ↓ Increasing wave length of the radiation absorbed	4000-4350	Violet	Yellow green
	4350-4800	Blue	Yellow
	4800-4900	Green blue	Orange
	4900-5000	Blue green	Red
	5000-5600	Green	Purple
	5600-5800	Yellow green	Violet
	5800-5950	Yellow	Blue
	5950-6050	Orange	Green blue
	6050-7500	Red	Blue green
			↑ Increasing depth of color of the object ↓

Complicated molecules such as those of most dyestuffs usually show several bands; or, absorption may be general over a fairly wide part of the spectrum. The color of such substances as observed directly gives little clue to the regions where they absorb. But the percentage absorption at selected wave lengths can be measured² with the spectrophotometer and the results plotted to show the absorption bands as illustrated in Figure 25-2.

25-3 Color and Constitution. In 1876, Witt summarized the information then available on the relationship between color and molecular

¹ *Depth* of color is not to be confused with the different *intensities* which a painter can obtain, for example, by mixing the pigments white lead and chrome yellow in various proportions.

² The extent of absorption by a solution depends upon the number of colored molecules in the path of the light. Hence, it is necessary to take into consideration both the concentration of the solution and the thickness of the layer examined. The position of an absorption band is reported in terms of its *head*—that is, the wave length which is absorbed most strongly.

structure and introduced two terms which are still widely used. Witt pointed out that every dyestuff contains an *unsaturated* group which he regarded as fundamentally responsible for its color. Such groups he called *chromophores*, meaning bearers of color. He further identified other groups which, while themselves incapable of producing color, can deepen it if the molecule contains a chromophore. These groups he

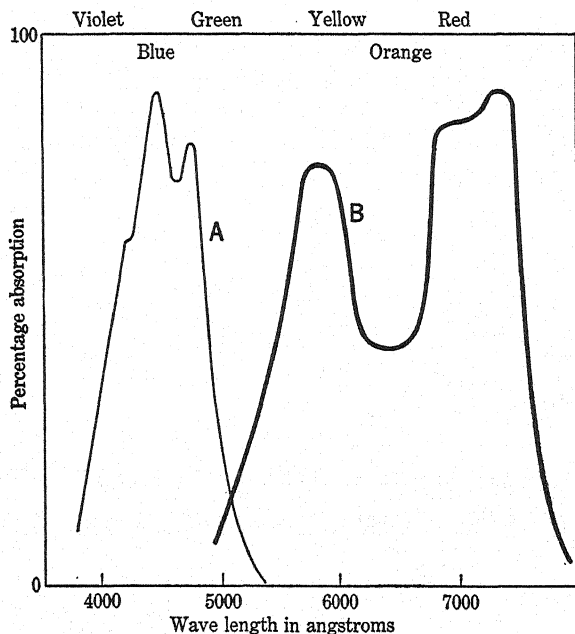


FIG. 25-2 Typical absorption curves. The height of the curve at any wave length measures the percentage absorption of that wave (in a solution of a specific concentration). Curve A, with its principal absorption maximum around 4500 Å, in the blue, is that of the orange-yellow plant pigment β -carotene. Curve B shows two distinct bands, with maxima in the yellow and red; the compound which gives it would probably be blue or green.

called *auxochromes*. To illustrate: Benzene, nitrobenzene, and aniline are all colorless, absorbing only in the ultraviolet; *p*-nitroaniline, which contains the chromophore NO_2 and the auxochrome NH_2 , is a deep yellow, almost orange, compound which absorbs in the visible spectrum up to about 4300 Å.

The groups now recognized as most important for the production and deepening of color are the following, arranged approximately in the order of decreasing effectiveness:

Chromophores			
$-\text{N}=\text{O}$	Nitroso	$\begin{array}{c} \text{H} \\ \\ -\text{C}=\text{N}- \\ \\ \text{O}^- \end{array}$	Azomethine
$\diagdown \text{C}=\text{S} \diagup$	Thio	$\begin{array}{c} \text{O}^- \\ \\ -\text{N}^+ \\ \\ \text{O} \end{array}$	Nitro
$-\text{N}=\text{N}-$	Azo	$\diagdown \text{C}=\text{O} \diagup$	Carbonyl
$-\text{N}=\text{N}^+-\text{O}^-$	Azoxy	$\diagdown \text{C}=\text{C} \diagup$	Ethylenic
Auxochromes			
$\begin{array}{c} \text{R} \\ \\ -\text{N}: \\ \\ \text{R} \end{array}$	$\begin{array}{c} \text{R} \\ \\ -\text{N}: \\ \\ \text{H} \end{array}$	$\begin{array}{c} \text{H} \\ \\ -\text{N}: \\ \\ \text{H} \end{array}$	$\begin{array}{c} \ddot{\text{O}}:\text{H} \\ \ddot{\text{O}} \end{array}$
			$\begin{array}{c} \ddot{\text{O}}:\text{R} \\ \ddot{\text{O}} \end{array}$

(where R is an *alkyl* radical, usually methyl or ethyl).

The decreasing effectiveness of chromophore groups suggested above is illustrated by the following compounds, in each of which two benzene rings are joined by a different chromophore:

Thiobenzophenone	$\text{C}_6\text{H}_5-\overset{\text{S}}{\overset{ }{\text{C}}}-\text{C}_6\text{H}_5$	Blue	6200 Å
Azobenzene	$\text{C}_6\text{H}_5-\text{N}=\text{N}-\text{C}_6\text{H}_5$	Orange	4500 Å
Benzalaniline	$\text{C}_6\text{H}_5-\overset{\text{H}}{\overset{ }{\text{C}}}=\text{N}-\text{C}_6\text{H}_5$	Colorless	3300 Å
Stilbene	$\text{C}_6\text{H}_5-\overset{\text{H}}{\overset{ }{\text{C}}}=\overset{\text{H}}{\overset{ }{\text{C}}}-\text{C}_6\text{H}_5$	Colorless	3100 Å

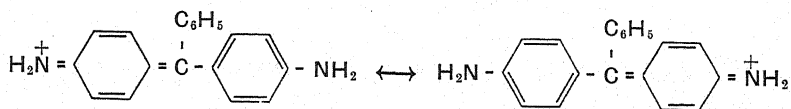
The values given in angstroms are the heads of the principal absorption bands. The thio group (in thiobenzophenone) is the most powerful of these four chromophores because it produces absorption at the longest wave length and, therefore, the deepest color (blue).

25-4 Color and Resonance. Radiation is a form of energy, and when matter absorbs radiation its energy is increased. This may be manifested by an increase in temperature,¹ or otherwise. When a molecule absorbs radiation, the added energy lifts it from the normal to what may be called an *excited* state. In this excited state a system of electrons oscillates with a frequency which is closely related to that of the waves absorbed. Color results if the oscillation path in the molecule is long

¹ The well-known effect of direct sunlight on a thermometer and the practice of wearing light-colored clothes in summer—because they absorb less radiation than dark ones—are commonplace examples.

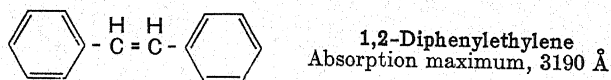
enough to synchronize with waves in the visible spectrum. According to modern views, *resonance* is the most important factor in providing long paths of electronic oscillations in molecules and, therefore, the most important factor in producing color.

Examining the above list of chromophores, it is seen that all of them are *meta*-directing groups which *withdraw* electrons from an aromatic nucleus (Sec. 22·8). Likewise we identify the important *auxochromes* with the most powerful *ortho*- and *para*-directing groups, which release electrons (Sec. 22·7). We have seen also how groups of these opposite types reinforce each other in promoting resonance in compounds such as *p*-nitroaniline and *p*-nitrophenol. Therein lies their relationship to color. Both nitrobenzene and aniline are colorless; but increased resonance toward ionic forms such as (IV) of Section 22·12 enables *p*-nitroaniline to absorb in the visible spectrum and thus exhibit its deep yellow color. Pure *p*-nitrophenol is colorless but gives yellow solution in alkalis because of the added resonance in the *p*-nitrophenoxide ion (Sec. 25·25). The much deeper color of many dyestuffs is associated with resonance between extreme forms in which a *unit* electrical charge can oscillate freely over a long path. This is well illustrated by the cation of Döbner's violet:



These forms are equivalent and equally probable; no separation of charge is involved, and there is no restraint on movement of the charge between the extreme positions.

25·5 Conjugated systems of double bonds play an extremely important role in producing deep colors by providing long resonance paths. This is illustrated by Döbner's violet and other dyestuffs in which the Kekulé "double bonds" of aromatic nuclei participate in the resonating system. It is illustrated also in the orange-red color of β -carotene (Sec. 4·13), which contains no aromatic nucleus but has a conjugated system of 11 ethylenic bonds. The isolated $\text{C}=\text{C}$ group is an extremely weak chromophore. Ethylene itself does not absorb waves longer than about 1800 Å, and even when the $\text{C}=\text{C}$ group is reinforced by two phenyl radicals a colorless compound is obtained:



But absorption shifts progressively to longer and longer waves as the number of $\text{C}=\text{C}$ bonds in a conjugated system increases. This is

shown by the following observations on a series of diphenylpolyenes:

Diphenylpolyene	Maximum absorption †, Å	Color†
$\text{C}_6\text{H}_5-\text{CH}=\text{CH}-\text{CH}=\text{CH}-\text{C}_6\text{H}_5$	3520	Colorless
$\text{C}_6\text{H}_5-(\text{CH}=\text{CH})_3-\text{C}_6\text{H}_5$	3770	Pale yellow
$\text{C}_6\text{H}_5-(\text{CH}=\text{CH})_4-\text{C}_6\text{H}_5$	4040	Greenish yellow
$\text{C}_6\text{H}_5-(\text{CH}=\text{CH})_5-\text{C}_6\text{H}_5$	4240	Orange
$\text{C}_6\text{H}_5-(\text{CH}=\text{CH})_6-\text{C}_6\text{H}_5$	4450	Brownish orange
$\text{C}_6\text{H}_5-(\text{CH}=\text{CH})_7-\text{C}_6\text{H}_5$	4650	Copper bronze
$\text{C}_6\text{H}_5-(\text{CH}=\text{CH})_{15}-\text{C}_6\text{H}_5$	5700	Greenish black

† Each of these compounds shows three characteristic absorption bands, of which only the one of longest wave length is indicated here. Because of these three bands the observed color cannot be predicted, but it is seen to deepen progressively.

These are results of the mobility of unsaturation electrons, already noted in connection with their polarizability (Sec. 3-8). *Concerted* movements of unsaturation electrons occur in conjugated systems. When these systems are extensive, the electron movements synchronize with long-wave radiation, which is absorbed, and deep color results.

The roles of chromophores, auxochromes, and conjugation in the production and deepening of color are further illustrated in connection with the dyestuffs considered below.

DYESTUFFS

25-6 Dyestuffs are colored substances capable of imparting their color to textile fibers in a dye bath. Among the many colored organic compounds that have the dyeing property, practical choice is made on the basis of cost of production, ease of application, and, more especially, fastness to light and washing. On account of their superiority in one or more of these respects, substantially all the dyestuffs used at present are synthetic compounds manufactured from aromatic hydrocarbons through their various intermediates.

The earlier synthetic dyestuffs were prepared more or less by chance. That is to say, various mixtures of organic compounds, selected somewhat at random, were heated or treated with some reagent in the hope that a colored compound with the dyeing property might result. When a number of dyes had been obtained in this way and their structures determined, it gradually became possible to formulate such relations as those expressed in Witt's chromophore theory. From these, chemists were able to predict compounds that might be expected to have the desired

properties and made systematic efforts to prepare them. Many of these efforts were successful, and some thousands of more or less satisfactory synthetic dyes were prepared. Those with the most desirable properties are today's commercial dyestuffs.

Classification. More than a thousand colored compounds are currently produced on a commercial scale in the United States. These may be classified according to similarities in chemical structure, as illustrated in Table 25-2. The most important classes are listed in this table and described in the paragraphs which follow.

TABLE 25-2 PRODUCTION OF DYES BY CHEMICAL CLASSES; USA, 1950

	Pounds
Azo.....	73,263,000
Triphenylmethane (and diphenylnaphthylmethane).....	7,597,000
Anthraquinone vat.....	42,526,000
Anthraquinone, other.....	6,288,000
Indigoid and thioindigoid.....	31,327,000
Sulfur or sulfide.....	24,038,000
All other dyes†.....	17,241,000
Total.....	202,280,000

† Includes among others: xanthene, stilbene, pyrazolone, azine, and thiazole dyes, most of which classes contain heterocyclic rings (Chap. 26).

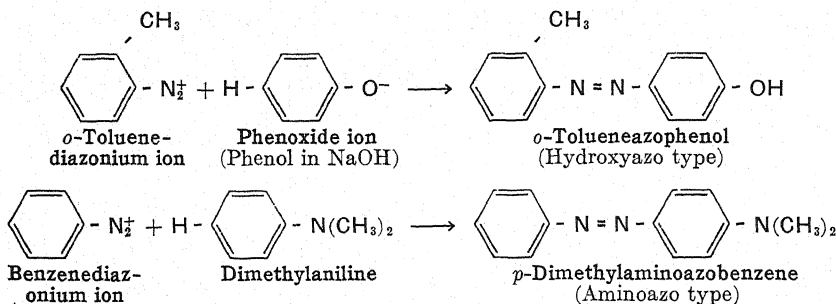
25-7 Historical. Since very early times man appears to have employed extracts of roots, barks, and other natural products to impart color to the fabrics used for clothing. The most important of these natural dyestuffs were Turkey red, obtained from the madder root, widely grown for this purpose in Asia Minor, and indigo, from a plant of the same name, which was even more widely cultivated in India and China. The royal or Tyrian purple of the ancients was obtained from a small sea snail found in the Mediterranean; about 12,000 snails are required to furnish 1.4 grams of the dyestuff—a very good reason for limiting its use to royal robes.

The first synthetic dyestuff was prepared by W. H. Perkin (Sir William Perkin) in 1856, while he was studying the action of oxidizing agents on crude aniline in an attempt to make quinine. Realizing the importance of his chance discovery, Perkin, then a student in the Royal College of Chemistry, London, began the manufacture of dyes on a commercial scale. His first dyestuff, known as *mauve* or *Perkin's violet*, has since been superseded by faster and more attractive colors.

Many other chemists took up the study of synthetic dyes, and progress was very rapid. In 1868, Graebe and Liebermann synthesized alizarin (Turkey red), and as this process was put on a commercial scale, the cultivation of madder in Asia Minor gradually disappeared. The synthesis of indigo took much more time, and the names of many chemists are associated with the story; but a number of different methods were developed, and today indigo is entirely a factory product (Sec. 25-14) and the natural source of historic interest only. A great variety of other synthetic dyes soon became available, exceeding in purity, low cost, range and brilliancy of color, and often in fastness, the natural products which they displaced. Developments still continue, to meet the special requirements for dyeing new artificial fibers such as cellulose acetate, nylon, and Orlon.

It is interesting to note that Tyrian purple has also been synthesized. It is not used commercially because it is less desirable than other dyes of the same color now available. One of its isomers is a commercial product commanding no higher price than most other dyes.

25-8 Azo dyes are made by diazotizing a primary aryl amine, as described in Section 13-16, and coupling (Sec. 25-9) the diazonium salt with a phenol or an amine. This yields *hydroxyazo* and *aminoazo* compounds, respectively, as illustrated by the following simple examples:

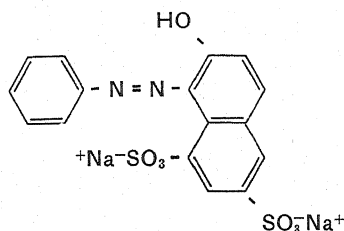


Both these compounds contain the azo chromophore and an auxochrome. They absorb strongly in the violet and blue and are colored yellow to orange in the solid state and in their alcoholic solutions; but they lack the other properties required of useful dyestuffs.

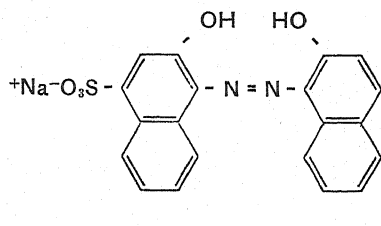
The substances coupled to form an azo color are called *components*. The first component—the one which is diazotized—may be almost any compound which contains a *primary* amino group, NH_2 , attached directly to an aromatic nucleus. The second component, with which the diazonium ion couples, can be selected from a wide variety of phenolic and arylamino compounds including secondary and tertiary amines of the types Ar.NHCH_3 and $\text{Ar.N}(\text{CH}_3)_2$. Hence, thousands of azo colors have been made in the laboratory. Several hundred are manufactured because they have the additional properties which make them useful. As a class the azo dyes exceed all others in variety, in the total quantity produced, and in aggregate value. They include dyes of substantially every color and shade.

Most azo colors used in textile dyeing are sodium salts of sulfonic acids.¹ The highly polar SO_3^- group imparts the solubility in water which is necessary in preparing the dye bath and has little influence on color. These dyes are made by using mono- or disulfonic acids as coupling components. This is illustrated in the manufacture of orange G and chrome blue black R, both of which are important textile dyes:

¹ The water-insoluble azo dyes used with acetate rayon and nylon (Sec. 25-22) are exceptions to this statement.



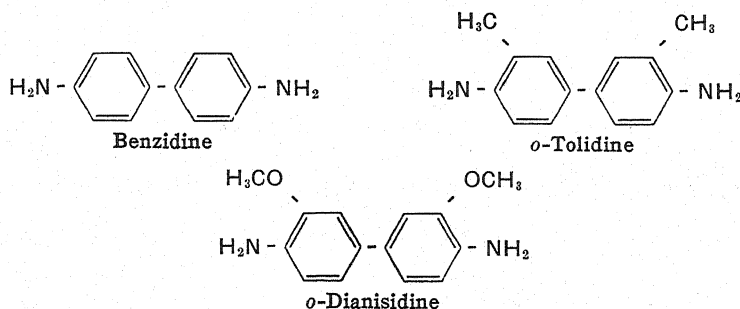
Aniline is diazotized and coupled with G acid (2-naphthol-6,8-disulfonic acid).



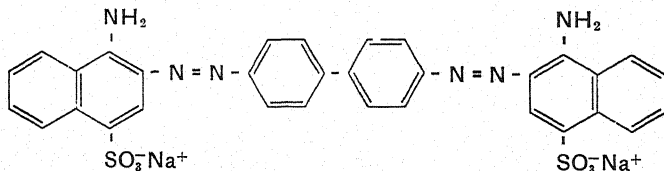
1:2:4 Acid (1-amino-2-naphthol-4-sulfonic acid) is diazotized and coupled with β -naphthol.

These two compounds also illustrate the fact that a great many azo dyes contain one or more naphthalene rings, which tend to deepen color. The major use of naphthalene substitution products (Table 24.1) is for the manufacture of azo dyes.

Polyazo Dyes. Another way to deepen color is to repeat the azo chromophore. Benzidine, *o*-tolidine, and *o*-dianisidine are important



first components for this purpose because they can be tetrazotized (*i.e.*, both NH_2 groups diazotized) and coupled at both ends of the molecule. This is illustrated in the manufacture of the disazo¹ color Congo red:

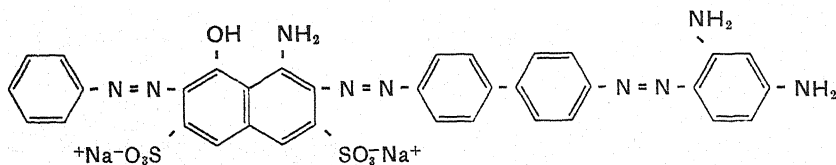


Benzidine is tetrazotized and coupled with two molecules of naphthionic acid (4-amino-1-naphthalenesulfonic acid).

One of the more important second components is H acid (8-amino-1-naphthol-3,6-disulfonic acid). This couples in the 7 position, adjacent

¹Compounds containing two, three, and four azo linkages are described as *dis-*, *tris-*, and *tetrakisazo*, respectively.

to the NH_2 group, in acid solution and in the 2 position, adjacent to the OH group, in alkaline solution. It is used, for example, in manufacturing direct black EW, which is produced in larger quantity than any other azo dyestuff:



Direct Black EW (a trisazo dyestuff)

Benzidine is tetrazotized and coupled with H acid in acid solution, adjacent to the NH_2 group; diazotized aniline is then coupled in alkaline solution, adjacent to OH of the H acid component; finally, the other diazotized group of the benzidine unit is coupled with *m*-phenylenediamine.

The special importance of the polyazo dyes lies in the fact that many of them are direct to cotton and viscose rayon (Sec. 25-20).

25-9 Coupling. The active agent in coupling is the diazonium ion, Ar.N_2^+ , which is deficient by one electron. The diazonium ion acts like other electrophilic agents (Sec. 22-5) in attacking an atom which has a readily available electron pair—that is to say, an atom with a relatively high $-\delta$ charge. Nuclear carbon atoms *para* and *ortho* to OH or NH_2 (NHR , NR_2) meet this requirement. This explains why the second component in making an azo dye is usually¹ either phenolic or an aryl amine.

In the benzene series the diazonium ion attacks, and coupling occurs in the position *para* to OH or NH_2 , if this is unoccupied, otherwise in the *ortho* position. Coupling in the unactivated *meta* position has never been observed. Naphthalene derivatives with OH or NH_2 in the 1 (α) position may couple at 2 or at 4; if the OH or NH_2 is at 2 (β), coupling occurs at 1; there are, however, many exceptions.

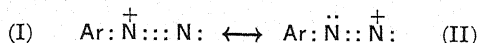
In diazotization (Sec. 13-16) an amine is usually dissolved in a considerable excess of strong hydrochloric or sulfuric acid. To couple with a phenol, this acid solution of the diazonium salt is poured into a solution of the phenol in an excess of sodium hydroxide—more than enough to neutralize the acid. Such an alkaline solution promotes coupling because its phenoxide ions carry a higher $-\delta$ charge on C^4 than does the phenol molecule (cf. Sec. 22-11) and are therefore more susceptible to electrophilic attack by the diazonium ion.

Before coupling with an amine the acidity of the diazonium salt solution is reduced quite low, to around pH 6, by adding sodium carbonate

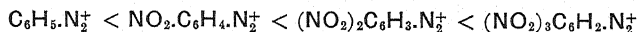
¹ Certain other compounds, such as methylphenylpyrazolone (Sec. 26-12), have an activated position at which a diazonium ion may displace hydrogen.

and sodium acetate. Amines do not couple at high acidity¹ because they are then in the form of ions, Ar.NH_3^+ . The plus charge on nitrogen in such an ion makes it electron *attracting*, and the *ortho* and *para* positions are deactivated. Reducing the acidity converts Ar.NH_3^+ into Ar.NH_2 , in which the NH_2 exercises its usual function of increasing electron density on C^4 , C^2 , and C^6 .

The ease of coupling is affected also by the structure of the first component—the substance diazotized. As explained previously (Sec. 13-16), the diazonium ion is a resonance hybrid with the extreme forms

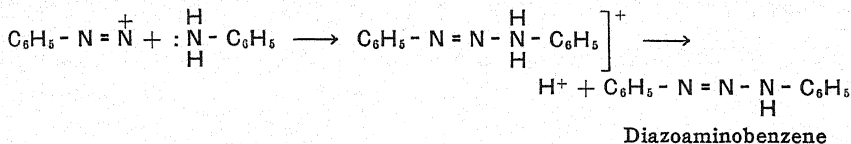


In coupling it acts as (II), which is favored by electron-attracting groups on the nucleus. Thus the ease of coupling increases greatly from left to right in the sequence



The practical advantage is greatly restricted by the fact that aryl amines containing electronegative groups are hard to diazotize.

25-10 Diazoamino Compounds. When a diazonium ion couples with a primary aryl amine or a secondary amine such as *N*-methylaniline, reaction usually begins with an attack on the *nitrogen* atom rather than upon nuclear carbon, because the former is the point of greatest electron density. For example,

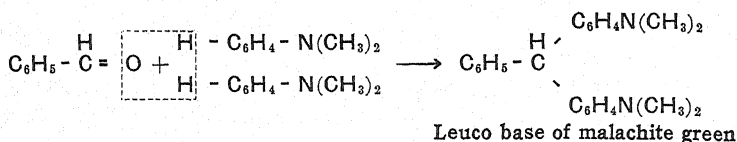


This particular compound is readily prepared, as follows. A given quantity of aniline is dissolved in an excess of cold acid, and one-half of its equivalent of sodium nitrite is added, thus diazotizing half of the amine. Acidity is then reduced by adding sodium acetate, whereupon the diazonium ion couples with the remaining aniline according to the last equation above. Diazoaminobenzene is readily isolated, but when heated with a mixture of aniline and aniline hydrochloride, it is quickly converted into its isomer *p*-aminoazobenzene, $\text{C}_6\text{H}_5-\text{N}=\text{N}-\text{C}_6\text{H}_4-\text{NH}_2$. (This involves a cleavage, followed by a recombination.) Similarly, when diazotization and coupling are conducted in the usual way, the end product is the same as though the attack occurred initially at the *para* position of the primary or secondary amine.

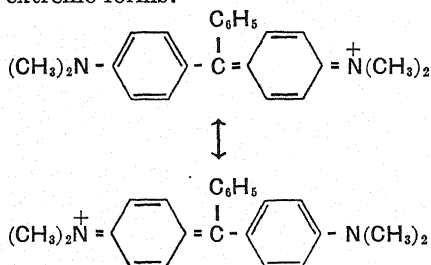
One practical use of diazoamino compounds is mentioned in connection with Rapidogen dyes (Sec. 25-21).

25-11 Triphenylmethane Dyes. Malachite green is one of the common dyestuffs of this class. It is made by condensing benzaldehyde with dimethylaniline in the presence of sulfuric acid:

¹ One reason for diazotizing at high acidity is to prevent the diazonium ion from coupling, as it is formed, with unreacted amine (cf. Sec. 25-10).



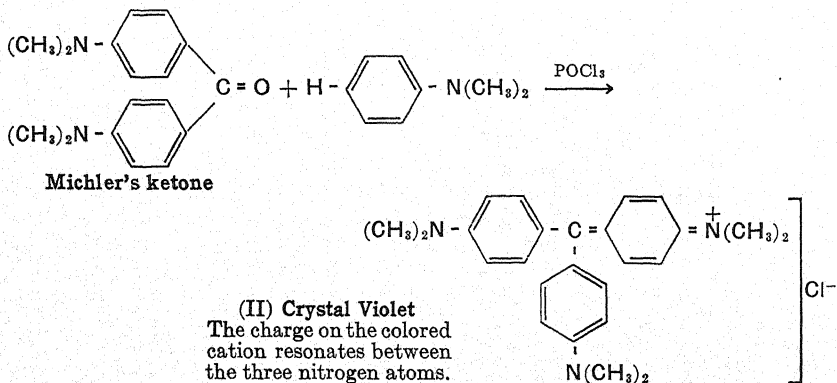
The product of this reaction, known as a leuco¹ base, is a colorless derivative of the hydrocarbon triphenylmethane. When dissolved in hydrochloric acid and treated with lead dioxide, the leuco base is oxidized to the dyestuff malachite green (I). This dyes silk and wool in bluish-green shades. The deep color of malachite green is due to an absorption band at 6169 Å (in the orange-red). Its ability to absorb such long waves is ascribed to resonance in the colored cation between the equivalent extreme forms:



(I) Malachite Green

The resonating cation. The dyestuff is usually sold as its oxalate or as the double salt with ZnCl_2 . Both salts form lustrous deep-green crystals which dissolve readily in water.

A larger group of dyes of this class is related to triaminotriphenylmethane, $(\text{H}_2\text{N} \cdot \text{C}_6\text{H}_4)_3\text{CH}$. This type is illustrated by crystal violet (II), in which all six of the N-hydrogen atoms are replaced by methyl groups.² Crystal violet is usually manufactured by condensing Michler's ketone and dimethylaniline with the aid of phosphorus oxychloride:



¹ From the Greek *leukos*, meaning white—that is, not colored.

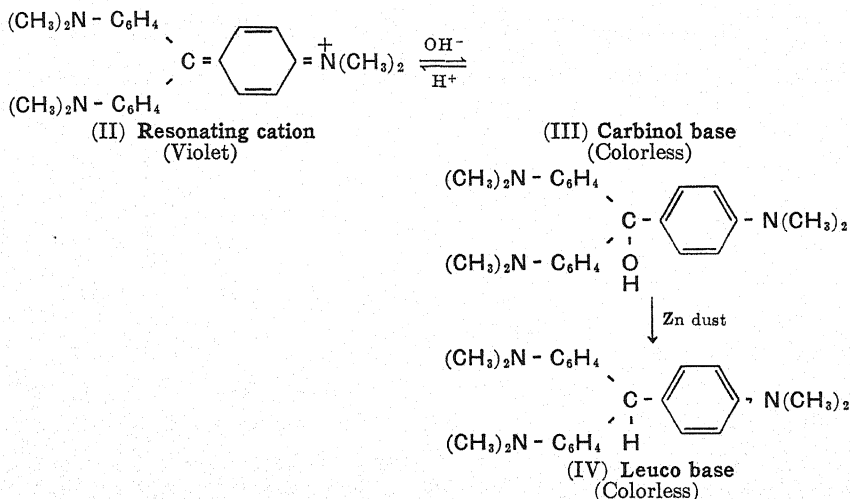
² Increasing numbers of methyl groups intensify the color and shift the shade from red toward blue. The dyestuff known as methyl violet is a mixture of the chlorides of crystal violet and related compounds containing four and five methyl groups.

The solid chloride consists of bronzy-green crystals which dissolve freely in water to give a deep violet solution. This color, due to absorption bands at 5910 and 5405 Å, is imparted directly to silk and wool.

The triphenylmethane dyestuffs (with which are included some related to diphenylnaphthylmethane) constitute the most important class of *basic* dyes (Sec. 25·18), in which the color is carried by a positive ion. They are very intense colors, unsurpassed for brilliancy and purity of tone, but fade rapidly in light. On account of the latter property, they are no longer much used on textiles, but large quantities are still produced and used for coloring paper, typewriter ribbons, and other articles where fastness to light is not too important.

Certain triphenylmethane dyes are sulfonated, by treatment with fuming sulfuric acid, and thus converted into acid dyes. These are sold and used as their sodium salts.

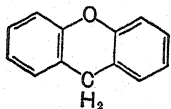
25·12 When alkali is added to a water solution of crystal violet, the color fades (somewhat slowly) and colorless flakes appear. This product is the carbinol base of crystal violet (III), which is formed by nucleophilic attack of hydroxyl ion on the methane (central) carbon atom. This union with hydroxyl destroys the resonance which is responsible for the color of the ion (II). When the solution is acidified, the color slowly reappears, showing that the change from (II) to (III) is reversible and depends upon the pH of the solution:



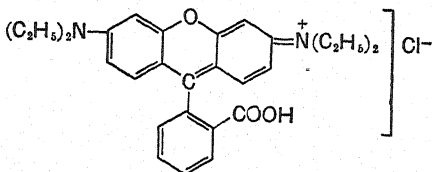
If a solution of crystal violet is warmed with zinc dust, the color disappears and does not develop again. This is the result of reduction to the leuco base (IV). Reduction cannot be reversed except by the action of a suitable, relatively strong oxidizing agent.

The relations just outlined between crystal violet and its carbinol and leuco bases are typical for other triphenylmethane dyes.

25.13 Xanthene dyes are, structurally, derivatives of the colorless heterocyclic compound xanthene (I). The amino derivatives are basic dyes called *rhodamines*. An example is rhodamine B (II), a red dye used mainly on paper.

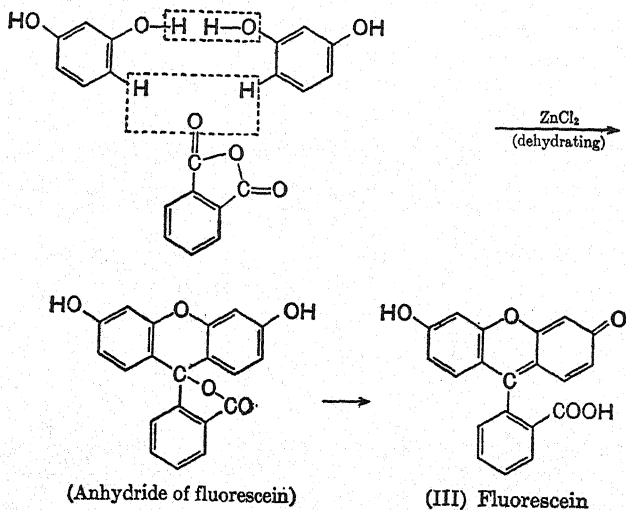


(I) Xanthene, $C_{13}H_{10}O$
(colorless)



(II) Rhodamine B

Phthaleins, or hydroxyxanthenes, are acid dyes of greater interest. The simplest phthalein dyestuff,¹ *fluorescein*, is made by condensing phthalic anhydride and resorcinol (two molecules) with the aid of zinc chloride. The xanthene ring is established by the elimination of two molecules of water, as follows:

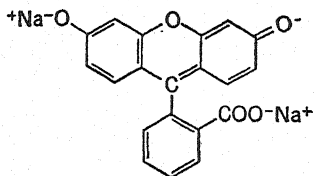


Fluorescein (III) is practically insoluble in water but forms a readily soluble sodium salt (IV). It gets its name from the intense fluorescence of its solutions in alkalis. This makes possible the detection of very minute quantities, and the sodium salt, *uranine*, has been used in tracing underground water and is provided aviators for showing the positions

¹ The simplest phthalein, *phenolphthalein*, is not a xanthene derivative and is colorless. It is used as an acid-base indicator (Sec. 25.27) and in medicine, as a cathartic.

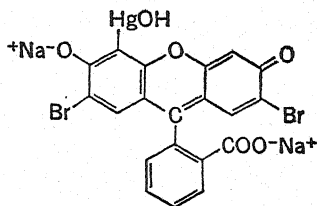
of life rafts if forced down at sea. Solutions are greenish yellow by transmitted and bright green by reflected light. Fluorescein dyes silk and wool yellow from an acid bath but is not fast enough to be useful.

The principal importance of fluorescein in the color industry is for conversion into more useful dyes and stains by halogen substitution. The four positions *ortho* to the OH groups are reactive and readily substituted by bromine and by iodine. Eosine G, the disodium salt of tetrabromofluorescein, is used extensively as a pink dye on silk. The corresponding tetraiodo compound is erythrosine. The antiseptic merbromin (V) is also a substituted fluorescein.



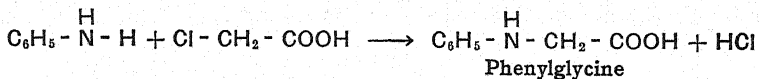
(IV) Fluorescein disodium salt; Uranine

The negative charge on the phenolic oxygen resonates as in the colored ion of phenolphthalein (Sec. 25-27).



(V) Merbromin; Mercurochrome

25-14 Indigo, one of the oldest known dyestuffs, is still used in very large quantities. The principal method of production starts with phenylglycine, which can be made¹ from aniline and chloroacetic acid:

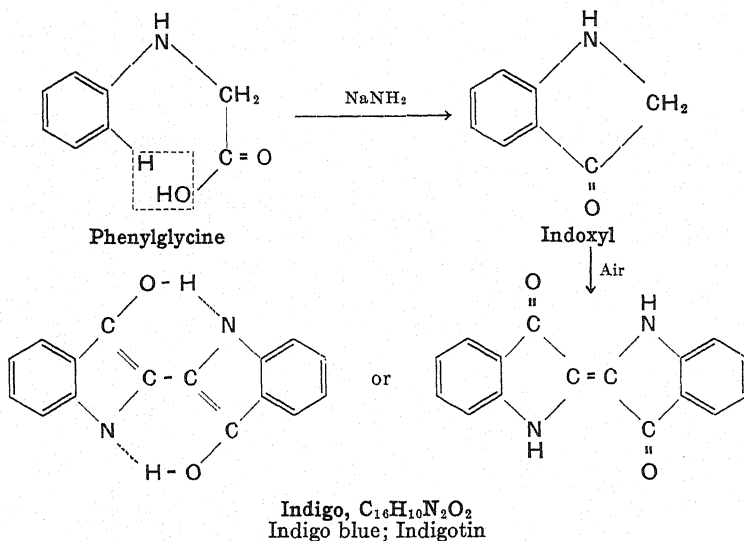


Sodium phenylglycinate is converted into indoxyl by heating at about 200°C with a fusion mixture of sodium and potassium hydroxides and sodamide, NaNH₂. After the ring closure effected by the fusion, water is added and air blown through. This effects the condensation of two molecules of indoxyl to insoluble indigo, which precipitates and is filtered out. The chelated formula represents an enol form stabilized by hydrogen bonding. It shows a conjugated system of double bonds, involving both benzene rings, which is doubtless related to the color. As a matter of fact, however, the depth of the indigo color cannot be explained adequately except by some extension of current theories.

Indigo is a dark blue crystalline powder with bronze luster (m.p. 390 to 392°C). It is soluble in aniline, nitrobenzene, chloroform, glacial acetic acid, and concentrated sulfuric acid but is insoluble in water and in

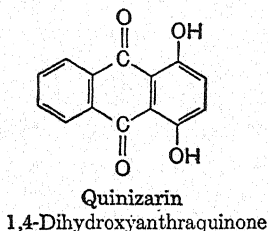
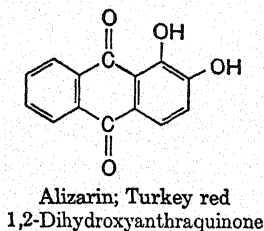
¹ A more important industrial method consists in adding aniline and sodium cyanide to a solution of sodium bisulfite and formaldehyde. This yields the nitrile of phenylglycine, which is hydrolyzed by alkali to a salt of the acid.

alcohol. Indigo is used in printing inks and, very extensively, for dyeing cotton, to which it is applied by the vat process (Sec. 25·23). Its dark blue color is extremely fast to all color-destroying agents, but the shade is dull and unattractive.



More desirable shades are obtainable in the related *indigoids*. Most of these are made by chlorinating or brominating indigo; or, one may replace aniline in the phenylglycine synthesis by *o*-toluidine, or some similar amine. The *thioindigoids* (which furnish blue-reds) are compounds in which the two NH groups of indigo are replaced by sulfur atoms.

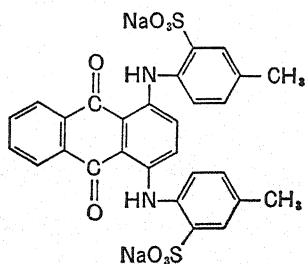
25·15 Anthraquinone Dyes. The oldest dyestuff of this class is alizarin (Turkey red, Sec. 25·7). It is manufactured by heating anthraquinone with fuming sulfuric acid; this yields 2-anthraquinonesulfonic acid, which is separated as its sodium salt. The salt is heated under pressure at $185^{\circ}C$ with a concentrated solution of NaOH and an oxidizing agent such as potassium chlorate. The sulfonic acid group is thus



replaced by OH, as is usual, and a second OH group enters in the 1 position.

Hydroxyanthraquinones containing two to six OH groups have been made and used either as dyes or as intermediates for better dyes. These include *anthrarufin*, 1,5-dihydroxyanthraquinone, and *quinizarin*. The latter is made by condensing phthalic anhydride with *p*-chlorophenol (Sec. 24·13), the chlorine atom exchanging for hydroxyl during the process. It is not a useful dye but is used in making others such as alizarin cyanine green. Alizarin and the other hydroxyanthraquinones cannot be applied to textiles except with the aid of a mordant and are little used at the present time.

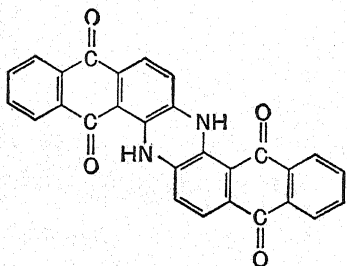
Anthraquinone acid dyes are direct to protein fibers and are used extensively on wools. Alizarin cyanine green is a typical example. It is produced by reducing quinizarin (see the last equation of Section 24·13), condensing with two molecular equivalents of *p*-toluidine, oxidizing to the keto form, and sulfonating with oleum.



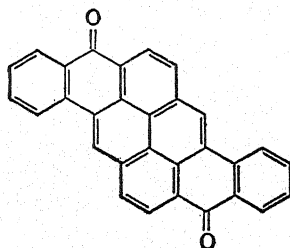
Alizarin cyanine green

The fastness of the anthraquinone acid dyes is increased and, often, their shades are improved by "chroming" (Sec. 25·19).

Anthraquinone vat dyes are by far the most important type related to anthraquinone and constitute one of the major classes of present-day textile dyes. They are available in many brilliant colors and shades of exceptional fastness. As indicated by the two examples which follow,



Anthraquinone Vat Blue RS
(Indanthrone)



Anthraquinone Vat Golden Orange G
(Pyranthrone)

the anthraquinone vat dyes are very complex and the reactions involved in making them are beyond the scope of this text. In the dyeing process (Sec. 25-23) these vat colors are reduced and oxidized in reactions similar to those indicated in the last equation of Section 24-13.

25-16 Sulfur dyes are usually manufactured by heating various nitrogenous aromatic compounds with sulfur or sodium polysulfide. Suitable raw materials include *p*-aminophenol, 2,4-dinitrophenol, a mixture of phenol with *p*-aminodimethylaniline, and derivatives of *p*-hydroxydiphenylamine. Very little is known with certainty about the chemical structures of the resulting dyestuffs; most of them are mixtures.

The sulfur dyes as a class are cheaper than any others and for this reason are manufactured in large amounts. They are used principally on cotton to impart heavy shades of blue, green, black, and brown (*e.g.*, khaki or olive-drab cotton uniform cloth). In general, they are reasonably fast to light and ordinary washing but not to the hypochlorite solutions now so widely used in laundries.

DYEING

25-17 The most important use of colored organic compounds is for imparting color to textile fibers in the form of yarn or cloth. Other major uses include leather dyeing and coloring paper, rubber goods, and synthetic plastics of every sort. Textile dyeing is usually accomplished by digesting the suitably prepared¹ cloth or yarn in a warm bath in which the dyestuff is either dissolved (molecularly dispersed) or colloiddally dispersed. Differences in the chemical natures of the fibers and of the dyes lead to certain major variations in the methods of application, some of which are described below. Dyes are classified from this practical standpoint as shown in Table 25-3.

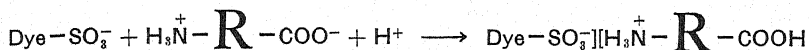
TABLE 25-3 DYES CLASSIFIED BY MODE OF APPLICATION

Percentage by weight of each class produced, USA, 1950

Acetate rayon and nylon.....	4.3	
Acid.....	10.4	
Azoic.....	4.1	
Basic.....	4.1	
Direct.....	20.3	
Sulfur.....	11.9	
Vat:		
Indigo.....	12.9	} 37.0
Other vat dyes.....	24.1	
All other synthetic dyes.....	7.9	

¹ Steps in the necessary preparation include cleansing, bleaching, and the application of surface-active agents (Sec. 16-21) which assist wetting and penetration of the fibers by the dyestuff. These and many details of the composition of the dye bath, its pH, the temperature and duration of heating, etc., are of utmost importance in practical dyeing but cannot be considered here.

25-18 Acid and Basic Dyes. Most acid dyes are sodium salts of sulfonic acids. They may be represented by the type formula $\text{Dye}.\text{SO}_3^-\text{Na}^+$, which indicates that the color is carried by a *negative* ion. Basic dyes (*e.g.*, crystal violet, rhodamine B) are salts of the general type formula $\text{Dye}.\text{NH}_3^+\text{Cl}^-$, in which the *positive* ion is colored. *Protein* fibers are permanently dyed by both classes by the simple process of heating in a water solution of the dyestuff. It is generally assumed that the process is fundamentally salt formation between colored ions of the dye and groups of the opposite charge in the fiber proteins (Sec. 21-15). Thus for an acid dye, which is applied in an acidic bath:



Acid dyes are used extensively on woolens and silk, basic dyes only rarely. Neither type will dye cotton except with the aid of a mordant.

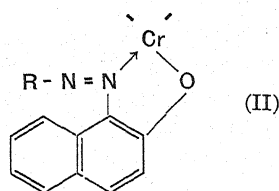
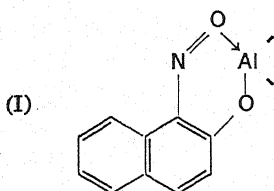
Biological stains, for better defining the microscopic structure of cells and tissues, are invaluable aids in histology, pathology, and other branches of medical science. They are either acid dyes (*e.g.*, eosine, acid fuchsin) or basic dyes (methylene blue, gentian violet, safranin, etc.) and probably react with tissue proteins in the manner described above for dyeing protein fibers.

25-19 Mordant and Chrome Dyes. The most important application of mordant¹ dyeing at the present time is the use of chromic hydroxide in connection with acid dyes on woolens. This increases fastness to washing and often improves the color. For example, chrome blue black R (Sec. 25-8) dyes wool a reddish-brown which is not particularly desirable. If the dyed fabric is further treated with a dichromate solution, under conditions favoring reduction to chromic hydroxide, the color is changed to a dead black of superior fastness. This method is called *after chroming*. Sometimes the chromic hydroxide is precipitated on the fibers before dyeing, and sometimes it is applied simultaneously with the dyestuff.

The union of an acid dyestuff with a basic, metallic hydroxide can be explained in terms of salt formation. This does not account, however, for the change in color, nor does it explain why mordants can be used to affix substantially neutral dyes such as alizarin and α -nitroso- β -naph-

¹ The term mordant is derived from the Latin *mordere*, to bite, and was introduced to convey the idea of a substance which bites both into the fabric and into the dyestuff, thus holding them together. In the earliest application aluminum hydroxide was precipitated on cotton cloth, which was thus enabled to take up alizarin and give the color Turkey red. Synthetic acid and basic dyestuffs were also used formerly to dye cotton with the aid of suitable basic and acidic mordants, respectively. With the later development of direct and vat dyes, which give similar results more cheaply, mordant dyeing has largely disappeared except in the chroming of wool here described.

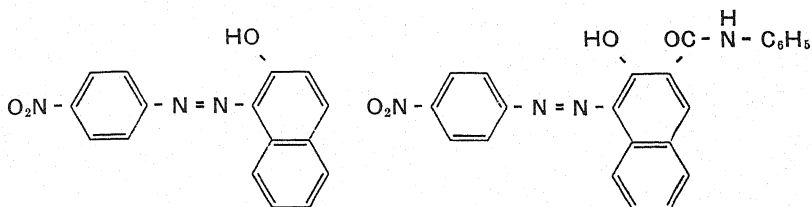
thol. There is strong evidence that these are bound by chelation of the metallic ion, as indicated in (I). Such complexes can be formed only by dyes so constituted that a five- or a six-membered ring results. This is possible when an OH group in the dyestuff is situated *ortho* to one of the groups: NO, NO₂, CO, OH, COOH, NH, NH₂, or N=N. The last combination indicated, found in the hydroxyazo dyes, is of special importance. Chelation in a compound of this kind is illustrated by (II).



25-20 Direct dyestuffs are those which dye *cotton* and regenerated cellulose without the aid of a mordant. They are also called *substantive* dyes. Virtually all are polyazo compounds containing SO₃H groups, used in the form of sodium salts. Direct black EW (Sec. 25-8) is a typical and important example. Most direct dyes are dispersed colloidally, rather than dissolved, in the dye baths. The latter contain relatively large amounts of salts such as sodium chloride and sodium sulfate (for which reason these dyes are sometimes called *salt colors*). It is believed that the direct dyes are affixed to the fibers by colloidal adsorption, which is favored by the high salt concentration; this serves also to decrease solubility of the dye.

The direct dyes are none too fast to washing. This fault is best corrected by the process called *development*. The fabric, dyed with a direct dye which contains an aryl NH₂ group, is passed through a bath in which nitrous acid is generated and the amino group diazotized. It then passes through rollers into another bath, containing a suitable second component (a naphthol, an arylenediamine, a pyrazolone) where coupling occurs. In this way a more complex and more insoluble azo dye is produced *upon and within the fibers*. Such development greatly improves fastness to washing and can be made to yield more desirable colors.

25-21 Azoic dyes are *insoluble* azo colors *produced on the fiber*. For example, cotton cloth may be soaked in an alkaline solution of β -naphthol, dried, and passed into an ice bath in which *p*-nitroaniline has been diazotized. Coupling of the components produces the highly insoluble para red (I) within and upon the fibers. Better results are obtained by using one of the naphthol AS compounds (Sec. 24-6) as the phenolic second component (II).



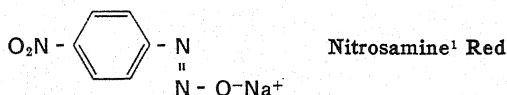
Para Red
(Diazotized *p*-nitroaniline is coupled with β -naphthol.)

Improved Para Red
(Diazotized *p*-nitroaniline is coupled with naphthol AS.)

One advantage of the naphthol AS compounds is their greater affinity for cotton, which adsorbs them more extensively than it does β -naphthol. Cotton treated with them need not be dried before passing into the coupling bath, and more level and permanent dyeing is possible.

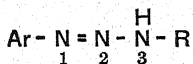
Azo dyes were formerly called *ice* colors. The use for ice was eliminated and convenience in dyeing increased by the discovery that certain diazonium salts (though not all) can be stabilized in dry condition for storage and shipment. Stabilized diazo compounds include double salts with zinc chloride ($\text{ArN}_2\text{Cl} \cdot \text{ZnCl}_2$) and salts of naphthalenesulfonic acids of the type (ArN_2^+)($\text{C}_{10}\text{H}_7\text{SO}_3^-$). These salts yield active diazonium ions when dissolved in water. Solutions are prepared as needed and used to develop azo colors on cloth impregnated with a naphthol AS.

Printing designs in azoic colors on cotton and viscose rayon is a widely used process. A stabilized diazo compound and a naphthol AS are made into a paste (with other suitable ingredients) and printed on the cloth from a roll engraved with the desired pattern. The cloth is then given an acid treatment, such as exposure to steam and the vapors of acetic acid. This liberates diazonium ions, which couple with naphthol AS on the fabric and produce color in the areas spotted by the paste. Many such prints compare favorably in fastness with those of vat dyes. The preparation of printing pastes requires more highly stabilized sources of diazonium ions than those described above. One major class (Rapid Fast Colors) consists of *antidiazotates* (Sec. 13-19) obtained by pouring the solution of a diazonium salt into a cold concentrated solution of sodium hydroxide. A simple example is



These compounds are made into pastes with a naphthol AS and alkali, printed, and then developed by an acid treatment which liberates diazonium ions.

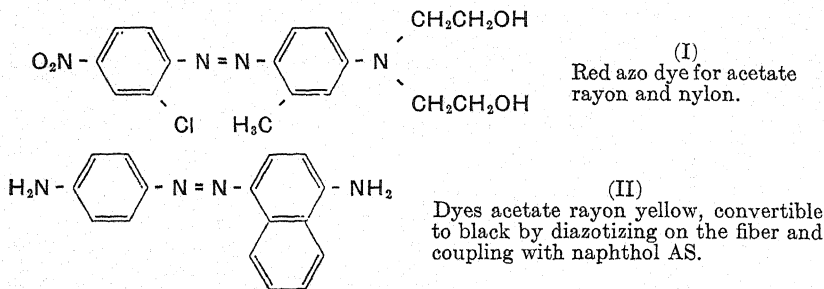
Rapidogens constitute the most recent class of stabilized azoics for printing. They are for the most part diazoamino compounds (Sec. 25-10) of the type



¹ These antidiazotates continue to be called "nitrosamines" in the dye industry, using a name based upon an earlier and mistaken view of their structures.

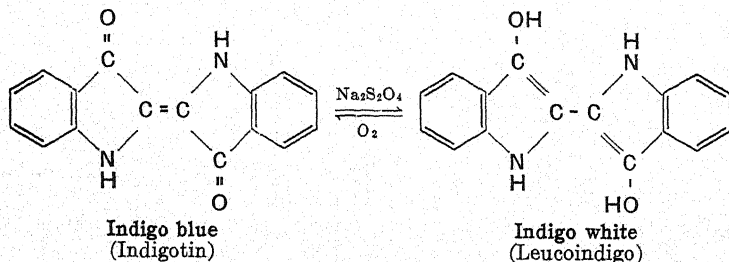
in which R carries a group which imparts water solubility. They are stable in alkaline solution but when acidified yield diazonium ions by cleavage between N^2 and N^3 .

25-22 Acetate-rayon and Nylon Dyes. These synthetic fibers cannot be dyed satisfactorily by the older dyestuffs or any of the older methods. The new dyes developed for use with them are water-insoluble compounds which are highly dispersed in the dye bath by soap or other surface-active agent. These dyes *dissolve* in nylon and cellulose acetate. Most of them are azo colors *without* SO_3H groups, such as (I) and (II):



25-23 Vat dyes are water-insoluble compounds which are applied to textile fibers by *reduction* to soluble forms. The reducing agent generally used is an alkaline solution of $Na_2S_2O_4$, commonly called sodium hydro-sulfite. The yarn or cloth to be dyed is soaked in the *vat*¹ thus prepared, so that the soluble, reduced molecules thoroughly permeate the fibers. After pressing out excess liquid the material is steamed and hung up for atmospheric oxidation or treated with some other oxidizing agent. In this way the oxidized, insoluble form of the dyestuff is regenerated within and upon the fibers.

Indigo is reduced in the alkaline vat to so-called indigo white (which actually gives a yellow vat):



The indigoids and thioindigoids go through similar changes. The oxidized and reduced forms of the anthraquinone vat dyes are related to

¹The term *vat*, as used in this connection, refers to such a reduced solution of the dyestuff and *not* to its container.

each other in the same way as anthraquinone and anthrahydroquinone (Sec. 24-13). Their vats are highly colored, but as a rule this color bears no close relation to that of the oxidized dyestuff.

Vat dyes are available in a great variety of brilliant colors and shades. They are exceptionally stable toward washing, light, laundry bleaches, and other color-destroying agents. This combination of properties accounts for their wide and increasing popularity.

Both the indigoids and the anthraquinone vat dyes are used for printing, in the form of water-soluble stabilized derivatives of their reduced forms. The sodium salts of their sulfate esters are often used (under trade names such as Leucosols, Indigosols, etc.). After printing with a suitable paste, color is developed on the cloth by treatment with an acid oxidant—*e.g.*, steam, air, and the vapors of acetic acid.

Sulfur dyes are essentially vat colors though they are usually classified separately and lack the fastness of those described above. They are insoluble in water but are reduced to soluble forms and dissolved by solutions of sodium sulfide. Cloth is soaked in the solution, pressed, and hung in the air for oxidation to the insoluble form. Sodium sulfide is a milder reducing agent than $\text{Na}_2\text{S}_2\text{O}_4$ and does not affect most indigoid and anthraquinone vat dyes.

25-24 Lake and Spirit-soluble Dyes. Color *lakes* are insoluble products made by precipitating a dyestuff upon an inorganic "carrier" such as zinc sulfide, barium sulfate, or China clay. One type of lake is obtained by precipitating aluminum hydroxide in a solution of an acid dye, which is carried down with the precipitate. Or, an insoluble azo dye can be formed by the usual coupling reaction while stirring with a suspension of a finely divided inorganic solid. *Toners* are pure water-insoluble dyes, not mixed with an inorganic carrier. Color lakes and toners are dried, usually ground in oil, and used like inorganic pigments in paints and lacquers, printing inks, and plastics.

Spirit-soluble and *oil-soluble* colors are compounds which are insoluble in water but dissolve in alcohol and in organic liquids of low polarity. They are used mainly to color alcohol varnishes, oils and fats, gasoline, etc. Most of them are azo compounds without SO_3H groups, *e.g.*, 1-phenylazo-2-naphthylamine, one of the certified food colors¹ used in oleomargarine. Oil red EG, the coloring matter generally used in gasoline and produced in large amounts for that purpose, is a disazo dye, made by diazotizing aminoazoxylene and coupling with β -naphthol.

ACID-BASE CHEMICAL INDICATORS

Certain organic compounds exhibit color changes in solution which are related directly to the hydrogen-ion concentration. Some of these are useful *indicators* in acid-base titrations and for colorimetric measurements of pH. The quantities consumed for such purposes are infinitesimally small in comparison with the tonnage used for dyeing. Nonetheless, such indicators are indispensable daily aids both in industrial control laboratories and in the development of chemical science through

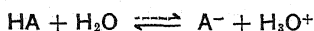
¹ The U.S. Federal Security Agency approves a limited list of dyes for use in foods, drugs, or cosmetics. They are harmless themselves when used for the permitted purposes and are certified as free from harmful impurities.

research. The study of a few of them contributes also to a better understanding of the relationship between constitution and color.

25-25 *p*-Nitrophenol is a typical single-color indicator. The solid consists of silky colorless crystals. It is colorless also (absorbs only in the ultraviolet) in 0.1 *N* hydrochloric acid, pH 1, and in other solutions of hydrogen-ion concentrations to about pH 5. With further decrease in acidity a faint yellow color develops and increases to a maximum intensity around pH 9. At intermediate pH values the intensity of the color varies with the extent to which colorless molecules are converted into yellow ions, as follows:

pH of solution.....	5.16	5.57	5.88	6.20	6.56	6.98	7.16	7.34	8.12	9.16
Colorless molecules, per cent....	99	97.5	95	90	80	60	50	40	10	1
Colored ions, per cent.....	1	2.5	5	10	20	40	50	60	90	99

p-Nitrophenol is a weak acid ($K_a = 6.9 \times 10^{-8}$) and, like all weak acids, its ionization depends upon the hydrogen-ion concentration of the solution:



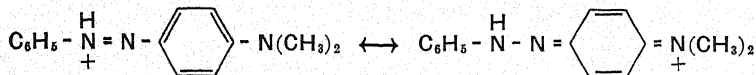
Equilibrium lies far to the left at high concentrations of H_3O^+ .



Equilibrium is displaced to the right, with formation of A^- ions, as the solution is made alkaline.

Resonance in the *p*-nitrophenoxide ion [formulas (III) and (IV) of Section 22-11] enables it to absorb light waves in the violet and blue. This produces the yellow color, which increases in intensity with the number of absorbing ions.

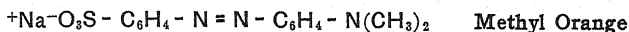
25-26 Azo indicators are illustrated most simply by *p*-dimethylaminoazobenzene. This compound is almost insoluble in water, but an alcoholic solution (Topfer's reagent) has been used in titrating the acidity of gastric juice. It forms orange crystals and is yellow in alkaline, neutral, and faintly acid solutions but gives a pink or red color at higher acidities (pH < 2.9). The yellow form is the molecule having the structure shown in Section 25-8; the two benzene rings linked by the $\text{N}=\text{N}$ chromophore permit enough resonance to absorb short visible rays, but resonance is restricted by the separation of charges which must accompany it. The red form is the hybrid cation



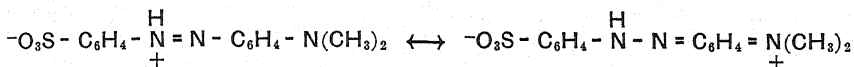
which is formed at higher acidities by addition of a proton. Movement

of the unit plus charge between the nitrogen atoms creates no restraining negative charge, hence the higher degree of resonance and the resulting absorption of longer waves.

Methyl orange, a more widely used azo indicator, is made by coupling dimethylaniline with diazotized sulfanilic acid, which provides a solubilizing sulfonate group:

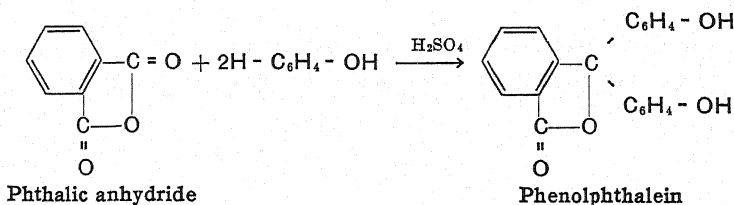


The color changes are like those of Topfer's reagent and originate in the same way. The red form is the hybrid dipolar ion (or inner salt):



The end point taken in titrations (pH 3.7 to 3.8) is a salmon pink which appears when about one-third of the yellow indicator has been converted into these red ions.

25.27 Phthalein Indicators. Phenolphthalein, the most widely used indicator of this class, is a white powder almost insoluble in water but dissolving in ethyl alcohol. It is made by condensing phenol with phthalic anhydride in the presence of sulfuric acid or zinc chloride:



Phenolphthalein is colorless in acid and neutral solutions, develops a faint pink at pH 8.4 to 8.6 (the usual end point in titrations with it) and a deep purplish red around pH 10.† The structural changes involved in the development of color are summarized in Fig. 25-3. As the hydrogen-ion concentration is reduced by the addition of alkali, ionization is shifted toward formation of the *bivalent* anion, which alone is colored. Formula (IV) shows one extreme form of this anion; this is in resonance with an exactly equivalent form in which the oxygen atom of ring (2) carries the negative charge.

Similar condensations between phthalic anhydride and various phenols, such as thymol, yield other phthaleins; some of these serve as acid-base indicators with somewhat different color ranges. *Sulfonephthaleins* are

† In the presence of concentrated alkali, phenolphthalein again becomes colorless through further changes which will not be considered here.

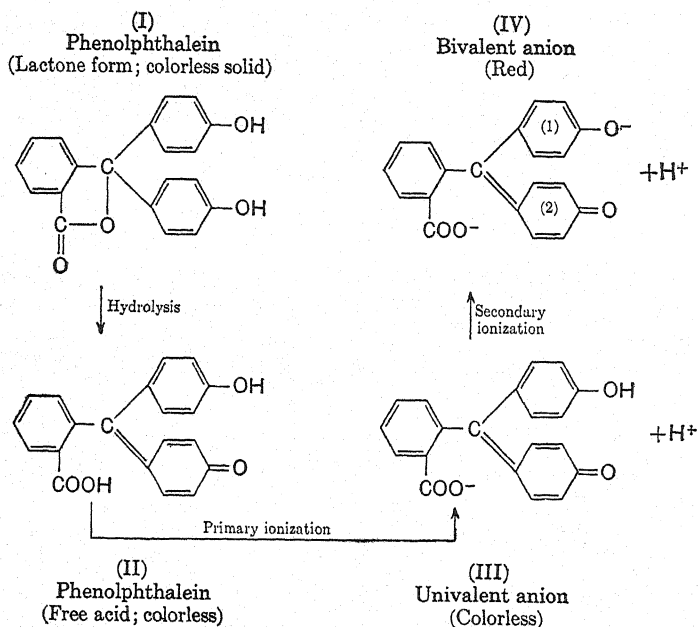
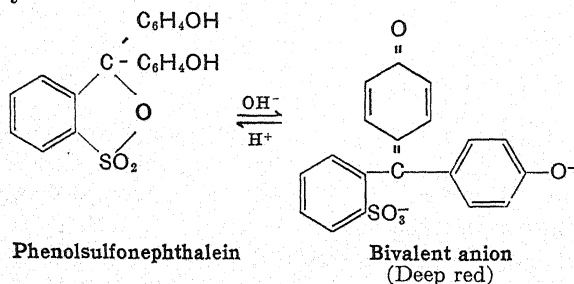


FIG. 25-3 Ionization of phenolphthalein; (IV) shows one of the two equivalent forms of the red hybrid anion.

obtained in like manner by condensing various phenols with *o*-sulfo-
benzoic anhydride:



The simplest member of this series, phenolsulfonephthalein, is yellow in acid solution but gives a deep red anion with alkalis. The others are likewise two-color indicators; the free acids and univalent anions have a light color (usually yellow) which changes to red, violet, blue, or green as acidity is reduced and highly resonating bivalent anions are formed. The sulfonephthalein indicators are characterized by brilliancy of color and relative fastness to light, for which reasons they are widely used in colorimetric measurements of pH.

Questions

1. (a) Give the quantitative relationship between wave length and frequency and relate both to the velocity of light. (b) Distinguish between visible, ultraviolet, and infrared radiation in terms of wave length and frequency. (c) Arrange the colors of the visible spectrum in the order of the increasing wave lengths of the radiation which produces them. (d) Arrange these colors in the order of increasing "depth."
2. Because frequencies of the order of 10^{14} are somewhat unwieldy figures, radiation is sometimes defined in terms of *wave numbers*—that is, the number of cycles which a wave completes in advancing a distance of 1 cm (10^8 \AA). Calculate the wave numbers of rays near the two ends of the visible spectrum ($\lambda = 4000$ and 7500 \AA).
3. Explain the sensation of color in terms of selective absorption of light.
4. (a) A certain substance is lemon yellow; if it has only one absorption band, in about what region of the spectrum does this occur? (b) Suppose it is converted into a derivative that absorbs only in the region about 5000 \AA ; what will be the color of the derivative? (c) From the observed colors of potassium chromate and of cupric sulfate solutions, which do you conclude exhibits absorption nearer the red end of the spectrum?
5. Define the terms "chromophore" and "auxochrome": (a) as they were used by Witt; (b) according to modern views. (c) Give examples of important chromophores and auxochromes, indicating specifically how they operate in the production and deepening of color.
6. Discuss, with examples, the relations between increase in resonance and increasing depth of color.
7. Write the structure of: (a) five compounds which can serve as a first component (Sec. 25-8) of azo colors; (b) five which can serve as a second but not as a first component; (c) five which can serve as either first or second components.
8. Selecting from the components you have listed above, or using others if necessary, write the equations for coupling reactions which would yield: (a) a hydroxyazo color; (b) an aminoazo color; (c) an azo color which you have a right to expect would be soluble in water; (d) an azo color which might be soluble in alcohol but not in water.
9. Check the coupling reactions written in question 8 to see that they follow the rules covering the *positions* at which coupling is to be expected.
10. On acidifying a deep violet solution of crystal violet the color changes to a rather pale yellow when two protons have been added to nitrogen atoms of the dye cation. Explain the change in color in terms of decrease in resonance.
11. Show and explain the relations between some triphenylmethane dyestuff, its carbinol base, and its leuco base.
12. (a) Write the structural equation for the preparation of fluorescein. (b) From the usual rules of directing influences, predict the positions taken by four substituting bromine atoms when fluorescein is converted into eosin. (c) Show that the phthalins obtained by the condensation of phthalic anhydride with monohydric phenols are not xanthene derivatives.
13. What properties other than color must a substance have in order to be a desirable dyestuff?
14. Summarize the different dyeing operations in which the color is fixed on the fiber: (a) by direct chemical union; (b) by an indirect chemical union; (c) by dissolving in the fiber substance; (d) by the diffusion of soluble substances within the fiber, followed by chemical conversion to an insoluble product.

15. (a) Using type formulas, write an equation showing the probable mode of reaction between an acid dyestuff and the protein of a wool or silk textile yarn, or the protein of some tissue intended for microscopic examination. (b) Do the same for a basic dye. (c) Reviewing the chemistry of the proteins, explain why a certain amount of free acid in the dye bath assists in affixing acid dyes to protein fibers.

16. Indicate two distinct ways in which an acid dye may unite with a basic mordant such as precipitated aluminum hydroxide.

17. Assuming that water-soluble substances can diffuse *into* and also *out of* cellulosic textile fibers, explain: (a) why a dyer cannot order para red from a manufacturer and apply it to his cloth; (b) how he *can* dye cloth with para red or "improved" para red; (c) why para red thus applied should be more stable to washing than the direct dye Congo red; (d) how certain direct dyes can be made more fast to washing by "developing" them on the fiber; (e) why the vat dyes (both indigoid and anthraquinone) are in general the most stable of all dyes to washing?

18. (a) Azo colors containing SO_3H groups and those without are both useful, but for different purposes. Illustrate and explain. (b) Comment on the possibility of using Congo red to color gasoline.

19. In connection with the use of *p*-nitrophenol as an acid-base indicator, explain accurately: (a) the origin of any color at all; (b) why and how the intensity of the color varies with the pH of the solution; (c) why there is no further increase in intensity at pH values greater than approximately 9?

20. Explain in terms of the possibilities for resonance why *o*-nitrophenol, which has the chelated structure shown in Sec. 23-10, is yellow in the solid state while *p*-nitrophenol crystals are colorless.

21. When an aqueous solution of picric acid is made alkaline, the yellow color is intensified. Explain fully, with the aid of appropriate structural formulas and ionic equations.

22. Account for the red and yellow colors of *p*-dimethylaminoazobenzene (or of methyl orange) and for the salmon-pink end-point color.

23. Write structural equations for the preparation of *o*-cresolphthalein and show the structural changes that account for the color it develops in alkaline solutions.

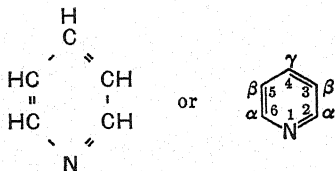
CHAPTER 26

HETEROCYCLIC COMPOUNDS

The aromatic and alicyclic hydrocarbons and their derivatives, containing *closed chains of carbon atoms only*, are described collectively as *homocyclic* (Gr., *homos*, same). In distinction, the term *heterocyclic* (Gr., *heteros*, different) is applied to organic compounds in which a ring system includes one or more noncarbon atoms. These *hetero* atoms are usually nitrogen, sulfur, or oxygen. Depending on the number of noncarbon atoms, such ring systems are classified as *monoheteroatomic* and *polyheteroatomic*. Rings with a total of five or six atoms are most common.

The above description includes the heterocyclic rings found in ethylene oxide, phthalic anhydride, the sugars, etc. These rings, however, are rather easily formed and are easily opened by hydrolysis and other simple reactions. The compounds containing them are studied most conveniently in connection with the open-chain molecules to which they are closely related. Certain other heterocyclic compounds, such as pyridine, have rings which are highly stabilized by resonance and properties which closely resemble those characteristic of benzene and other aromatic compounds.¹ Between this highly aromatic pyridine and the completely aliphatic ethylene oxide, there are heterocyclic compounds in great variety which are "more or less aromatic" in character.

26.1 Pyridine, C_5H_5N , may be regarded as a benzene molecule in which one CH group has been replaced by a nitrogen atom:

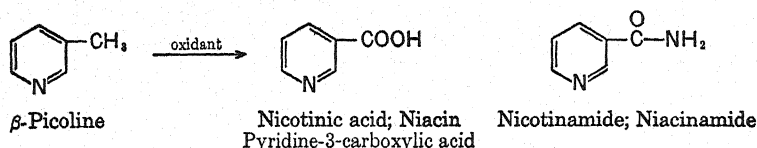


Pyridine
b.p. 115.3°

¹ If he has not done so already, a student should now prepare a summary of the properties specific to *aromatic* compounds. This should include both the characteristic reactions of the hydrocarbons and those of their distinctive derivatives, *e.g.*, the reactions peculiar to *aryl* amines and those in which phenols differ from alcohols. Evidence for resonance, and its consequences, should be considered.

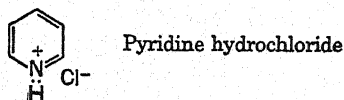
The six positions are designated either by numbers or by Greek letters as indicated. Pyridine occurs in coal tar, from which it is extracted by agitating with dilute sulfuric acid. The same source also yields the three monomethylpyridines, usually called α -, β -, and γ -picolines.

Aromatic properties are highly developed in pyridine and its homologues and many of their derivatives;¹ *e.g.*, 3-aminopyridine resembles aniline in that the NH_2 group yields a diazonium salt which couples normally and 3-chloropyridine resembles chlorobenzene in the firmness of its carbon-chlorine linkage. The pyridine nucleus is highly resistant to oxidation, while side chains are readily oxidized to carboxyl, *e.g.*,



Nicotinic acid, or its amide, is the antipellagra component of the vitamin B complex (Sec. 27-13). Both compounds are now manufactured and used extensively, under the names niacin and niacinamide, to correct dietary deficiencies. Nicotinic acid can be made by oxidizing β -picoline as indicated above and by oxidizing the alkaloid nicotine, a by-product of the tobacco industry; the latter was its original source and explains its name. It is usually manufactured from quinoline (Sec. 26-4).

26-2 Pyridine as an Amine. Pyridine is a weak base (with ionization constant $K_b = 1.4 \times 10^{-9}$), not much stronger than aniline, but forms stable crystalline salts with all strong acids, *e.g.*,

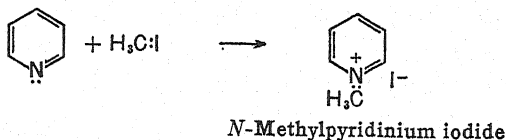


This property is utilized in the Schotten-Baumann and other reactions in which pyridine is added to bind protons as they are liberated.

Pyridine acts like a typical tertiary amine in combining with alkyl halides to form *pyridinium* quaternary salts.² Thus it reacts vigorously with methyl iodide:

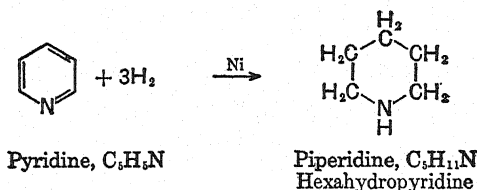
¹ Pyridine derivatives with groups in the β (3,5) positions resemble the corresponding benzene derivatives most closely. The behavior of groups in positions 2,4, and 6 is less certainly predictable; details are beyond the scope of this text.

² Industrial uses of pyridinium salts containing a long-chain radical such as C^{18} include the production of cation-active detergents and waterproofing agents for cloth (Zelan, Velan).



Many of the simpler pyridinium salts have well-defined melting points; otherwise, they closely resemble typical quaternary ammonium salts. They react with moist silver oxide to give solutions of pyridinium hydroxides which are strong bases. Niacinamide is combined as a pyridinium salt in Coenzyme I (Sec. 27·16).

Pyridine adds hydrogen more readily than does benzene and is thus reduced to piperidine:

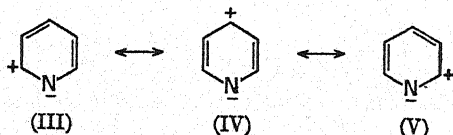


Piperidine is a base considerably stronger ($K_b = 1.6 \times 10^{-3}$) than ammonia, with all the other properties expected of a typical secondary *aliphatic* amine; the loss of resonance through saturation by hydrogen obliterates all aromatic properties.

26·3 Resonance of Pyridine. Heats of combustion indicate that pyridine is stabilized by resonance somewhat more than is benzene. Resonance is indicated also by the shortened bond lengths in the ring calculated from electron-diffraction measurements. The principal resonance forms are (I) and (II), which correspond to the Kekulé formulas for benzene:



The molecule also receives appreciable contributions from three other forms:

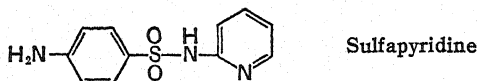


These ionic forms arise from the higher electronegativity of nitrogen, which results in a drift of carbon electrons toward it. Thus all the carbon

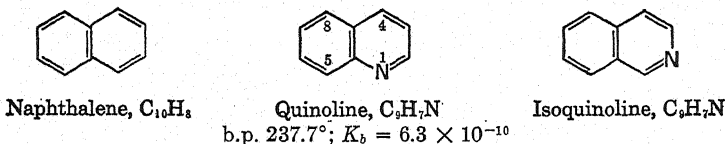
atoms are electron deficient as compared with those of benzene, and the effect is greatest on C², C⁴, and C⁶, which carry $+\delta$ charges.

Much of the chemistry of pyridine which was formerly confusing can now be explained in terms of what has just been stated, particularly the facts with regard to substitutions. Bromination, nitration, and sulfonation require much more drastic conditions than with benzene, and when these reactions occur it is in the β (3,5) positions. The reagents used are electrophilic (Sec. 22-5) and attack at points of relatively high electron density. Hence it is understandable why they attack pyridine with difficulty and, prevailing, at the β carbon atoms where electron deficiency is least. The situation is entirely comparable to that in nitrobenzene (Sec. 22-8), where the NO₂ group deactivates all ring positions by withdrawing electrons but acts least on the *meta* positions.

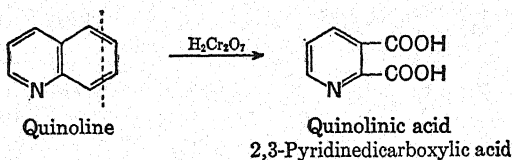
Conversely, *nucleophilic* reagents such as sodamide, NaNH₂, attack pyridine readily in the α (2,6) positions. This reaction with sodamide is used to produce 2-aminopyridine, required for the manufacture of the drug



26-4 Quinoline, which also is isolated from coal tar, contains a pyridine nucleus fused with a benzene nucleus as are the two benzene nuclei of naphthalene:



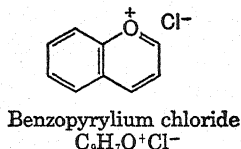
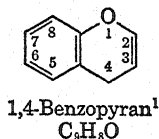
(The formula of isoquinoline is shown also for comparison.) As would be predicted from the behavior of pyridine, the benzene nucleus in quinoline is the more easily substituted; *e.g.*, nitration gives 5- and 8-nitroquinolines. The pyridine ring is easier to hydrogenate but more resistant to oxidation, *e.g.*,



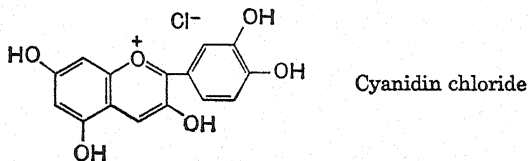
Quinolinic acid is decarboxylated in the 2 position by heating to 180°C ; this yields nicotinic acid, which is usually manufactured in this way.

The quinoline nucleus occurs in various alkaloids including quinine (Sec. 26.15), from which quinoline was first obtained, by destructive distillation, and named. Some synthetic drugs are also quinoline derivatives, *e.g.*, cinchophen, 2-phenylquinoline-4-carboxylic acid.

26.5 Pyran and benzopyran nuclei are encountered most frequently in the form of oxonium salts such as benzopyrylium chloride:



Among the most interesting derivatives are the red and blue flower pigments. The parent compound is a benzopyrylium salt such as cyanidin chloride:



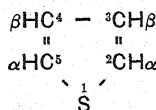
In the form of its glucoside, cyanidin chloride accounts for the colors of crimson flowers such as roses in which the cell sap is fairly acidic. In alkaline sap, cyanidin is converted into blue or purplish salts of its phenolic groups. Another series of compounds closely related to cyanidin are the *flavones*. These are yellow vegetable dyes which are widespread in nature, *e.g.*, in leaves, in tanbark, and in certain yellow flowers. In the fall of the year, when the green chlorophyll disappears, the flavones produce the autumn colorings.

It will be recalled that many of the sugars exist in so-called pyranose forms—that is, they contain rings of one oxygen and five carbon atoms and resemble pyran in this respect, though they lack its unsaturation.

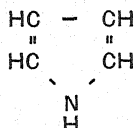
26.6 Five-Membered Rings. The simplest compounds of this class contain an unsaturated four-carbon chain closed by an atom of sulfur, or

¹ In the conventional formulas for heterocyclic compounds, a carbon atom is indicated by each angle where no N, S, or O is shown (cf. Sec. 5.6). It is understood, further, that enough hydrogen atoms are attached to satisfy the carbon valence of four. In 1,4-pyran, for example, three valence bonds extend to each of the positions 2, 3, 5, and 6; hence one hydrogen atom is counted at each of these positions. But only two valence bonds extend to C^4 , which carries two hydrogen atoms. C^4 likewise carries two hydrogen atoms in benzopyran—but *not* in a pyrylium compound.

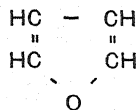
nitrogen (as NH), or oxygen. Structures are usually represented by the following formulas, in which the customary numbering and use of Greek letters are illustrated for thiophene:



Thiophene



Pyrrole



Furan

All are now regarded as resonance hybrids. The major form of each is that represented above, modified to a greater or less extent by contributions from forms such as those shown for pyrrole in Section 26-8. Resonance and aromaticity decrease in the order thiophene, pyrrole, furan. Naturally, both disappear when the rings are saturated by hydrogenation.

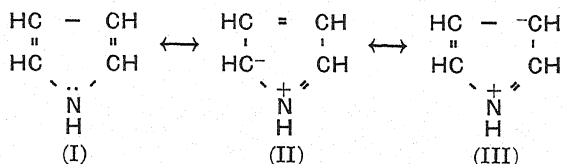
26-7 Thiophene, $\text{C}_4\text{H}_4\text{S}$, b.p. 84°C , is present in coal tar and light oil; benzene from this source always contains it unless especially purified. Purification is effected by shaking with concentrated sulfuric acid which sulfonates thiophene more readily than benzene and thus removes it. The resemblance between benzene and thiophene is remarkable, both in physical and chemical properties. Thiophene can be brominated without the aid of iron, it is nitrated readily, and its hydrogen atoms enter into the Friedel-Crafts reaction. It is interesting to note that the benzene ring in drugs such as cocaine can be replaced by a thiophene nucleus with little change in pharmacological properties. Thiophene can be made by heating sodium succinate with phosphorus trisulfide and also by a high-temperature reaction between *n*-butane and sulfur.

Thiophene and its derivatives give an intense blue coloration when treated with concentrated sulfuric acid and a trace of isatin. This *indophenine* reaction was long regarded as a characteristic property of *aromatic hydrocarbons* since it was given by all specimens obtained from coal tar. The chance observation that benzene prepared from pure benzoic acid did not give the indophenine test led Victor Meyer to the discovery of thiophene (1883).

26-8 Pyrrole, $\text{C}_4\text{H}_5\text{N}$, b.p. 131°C , can be isolated from coal tar and the oil obtained by the dry distillation of bones (Dippel's oil). The complex molecules of the blood pigment *hemoglobin* and the green leaf pigment *chlorophyll* contain similar combinations of four pyrrole nuclei. The amino acids proline and oxyproline (Table 21-1) and the alkaloid nicotine contain the reduced pyrrole (pyrrolidine) ring.

Both the physical and chemical properties of pyrrole point to a stabilization of the ring system by resonance, although to a less extent than in

thiophene. Present views are that the actual structure of the molecule approximates the Baeyer formula (I), modified to some extent by two forms in which an α carbon carries a negative charge (II) and, to a less extent, by two forms like (III) in which the negative charge is on a β carbon atom.



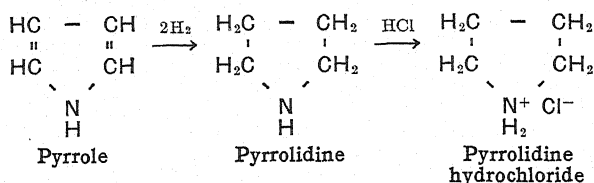
The Baeyer formula represents pyrrole as a typical secondary amine with the usual unshared electron pair on the nitrogen atom. In each ionic form this pair becomes involved in double bond formation, and the nitrogen atom acquires a positive charge as in the ammonium ion. Hence, through the contributions of the (II) and (III) forms, the actual state of the molecule must be such that the nitrogen atom carries a $+\delta$ charge and each carbon atom is a seat of higher than average electron density.

The chemical properties of pyrrole agree well with this conception of its structure. The substance gives substantially no evidence of basic properties—the $+\delta$ nitrogen atom cannot attract and bind a proton—but acts more like a weak acid. In this and other respects it bears a rather striking resemblance to phenol. This is true especially of the great ease with which the *C*-hydrogen atoms are substituted by the action of electrophilic reagents. It can be chlorinated by SO_2Cl_2 , brominated without the aid of iron, and is even iodinated readily (by the triiodide ion, I_3^-). It is acylated through the Friedel-Crafts reaction more easily than benzene and yields *C*-alkyl derivatives by the simple action of methyl iodide. Certain aminopyrroles can be diazotized and the *C*-hydrogen atoms of pyrrole and its derivatives are active enough to couple with diazonium salts, forming azo dyes. All these reactions with electrophilic reagents can be understood in terms of the higher electron density which resonance¹ imparts to the carbon atoms. The aliphatic properties to be expected from the conjugated diene system of the Baeyer formula (I) are illustrated by the ease with which pyrrole is polymerized by acids. This makes impossible such reactions as nitration and sulfonation.

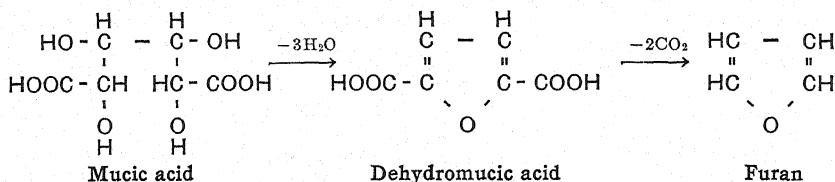
Pyrrole is reduced by hydrogen to pyrrolidine. This compound has an

¹ A more detailed study shows that the α positions are most reactive. This indicates that the forms represented by (II) contribute more than (III) to the state of the molecule.

ammoniacal odor, readily forms salts with acids, and otherwise resembles the aliphatic secondary amines.

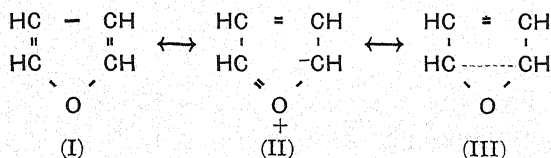


26-9 Furan, $\text{C}_4\text{H}_4\text{O}$, b.p. 31°C , is found in pine wood tar and can be made from various open-chain compounds such as mucic acid, an oxidation product of the sugar D-galactose:



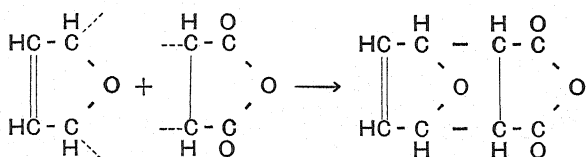
Furan is manufactured from furfural (Sec. 26-10). Aromatic properties are less evident than in any of the unsaturated heterocycles mentioned above. It is extremely sensitive to acids, which cause ring opening and polymerization. The latter reaction can occur explosively with furan and with its simple derivatives furfuryl alcohol and furfural. Ring opening also tends to occur during catalytic hydrogenation but can be minimized by avoiding high temperatures. However, furan does enter into aromatic substitution reactions not requiring acid conditions; it is acylated, for example, even more easily than benzene in a modified Friedel-Crafts reaction.¹ Negative substituents help stabilize the furan ring, *e.g.*, 2-furoic acid can be sulfonated.

The conventional formula for furan (I) is that of an unsaturated ether with conjugated ethylenic bonds. Its substitution reactions—which proceed most readily in the α (2,5) positions—point to a contribution from ionic forms (II). Polymerization and some well-defined 1,4-addition reactions indicate a contribution from (III):

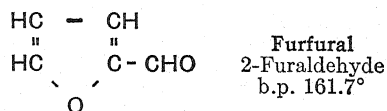


¹ Anhydrous SnCl_4 or ZnCl_2 is used instead of AlCl_3 . The tendency of AlCl_3 to accept an electron pair and complete its octet makes it a strong acid (in the sense used by Gilbert Lewis) and therefore useless with furan.

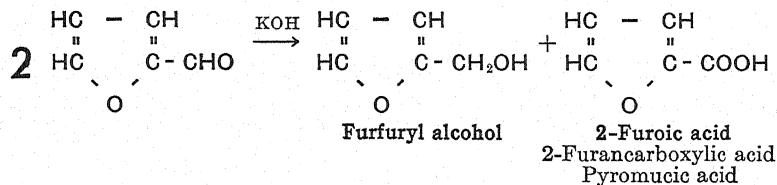
The last formula, showing a so-called "formal bond" between the α carbon atoms, is intended to suggest a situation comparable to that which leads to 1,4-addition reactions in butadiene. Furan resembles typical dienes in giving a normal addition product with maleic anhydride in the Diels-Alder reaction (Sec. 19-6):



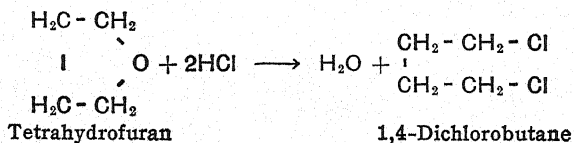
26-10 Furfural is related to furan as is benzaldehyde to benzene:



It closely resembles benzaldehyde in the chemical properties associated with the CHO group, *e.g.*, in oxidation of CHO to COOH and in entering into the Cannizzaro reaction with strong alkalis:

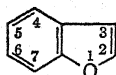


Furfural is manufactured cheaply and in large quantities from oat hulls and corncobs by digestion with acid and steam.¹ It is used as a solvent and for condensation with phenol in the manufacture of synthetic resins. Probably its most important use depends upon the sequence of reactions: oxidation to 2-furoic acid; decarboxylation to furan; and low-temperature hydrogenation to tetrahydrofuran. This cyclic ether is converted by hydrochloric acid into 1,4-dichlorobutane, an intermediate for the manufacture of nylon:

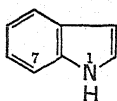


¹ The source of furfural is pentosan plant material (Sec. 18-13) which is hydrolyzed to pentose sugar; this in turn is dehydrated in a manner similar to mucic acid (Sec. 26-9).

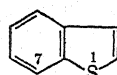
26-11 Fused Five-membered Rings. The following compounds and their derivatives contain a five-membered heterocyclic ring fused with a benzene nucleus:



Benzofuran, C_8H_6O
Coumarone

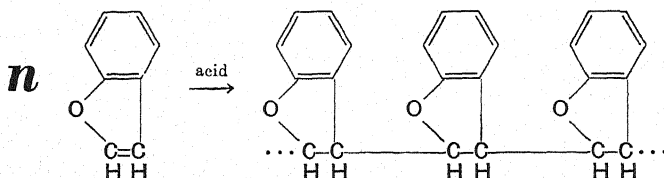


Indole, C_8H_7N
Benzopyrrole



Benzothiophene, C_8H_6S

The double bond shared by the two rings in benzofuran appears to be involved so completely in the resonance of the benzene nucleus that the five membered heterocyclic ring has little aromatic quality. Consequently, the $C^2=C^3$ double bond is more independent than in furan and shows typical unsaturation reactions, such as addition of bromine and polymerization. The latter reaction

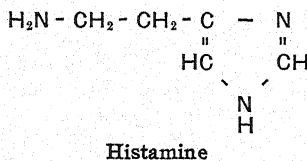
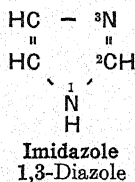


is involved in making the *coumarone-indene*¹ resins.

Indole is the structural parent of the amino acid tryptophane and of indigo. Benzothiophene bears this relationship to the thioindigoids.

26-12 Polyheterocycles, in which the ring contains more than one hetero atom, are numerous and varied. A few of the more common ring systems are shown below and further illustrated by the formulas of typical derivatives which contain them.

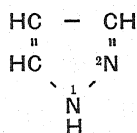
Imidazole (m.p. $90^\circ C$) is a structural parent of the amino acid histidine (Table 21-1) and of histamine, which is formed by decarboxylation of this acid:



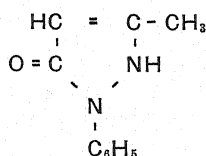
¹ Indene and coumarone (benzofuran) are contained in the solvent-naphtha distillate from coal tar. These two compounds are resinified (polymerized) by treating the purified naphtha with cold sulfuric acid, after which the volatile substances present are removed by distillation. The product is the least expensive type of synthetic resin. It is used in rubber compounding (as a softener), as a binder in floor tile, and in certain protective coatings. Indene, C_9H_8 , has the structure of benzofuran with CH in place of the oxygen atom.

Various allergies ("hay fever," asthma, etc.) have been treated successfully by the use of drugs called antihistaminics, which appear to inhibit the formation of histamine in the body.

The *pyrazole* nucleus occurs in oxidized form in the pyrazolones. These include the dyestuff tartrazine, the drug aminopyrine, and 3-methyl-1-phenyl-5-pyrazolone. The latter couples readily with diazonium ions and is a favorite second component for developing azo dyes on fabrics.

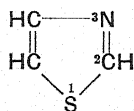


Pyrazole
1,2-Diazole

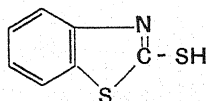


3-Methyl-1-phenyl-5-pyrazolone
Developer Z

Both sulfur and nitrogen are present in the five-membered ring of *thiazole*. This ring system is found in the drug sulfathiazole (where it is linked at its 2 position), in vitamin B₁ (thiamine, Sec. 27-14), in penicillin (Sec. 27-28), and in the important vulcanizing accelerator mercaptobenzothiazole:

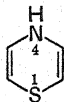


Thiazole

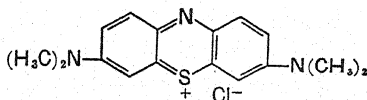


2-Mercaptobenzothiazole

The six-membered ring of 1,4-*thiazine* likewise contains nitrogen and sulfur. It is present in the dyestuff and stain, methylene blue:



1,4-Thiazine, C₄H₆NS

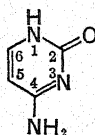


Methylene blue

The *pyrimidine* nucleus is present in the drugs sulfadiazine and sulfamerazine, in thiamine, and in the pyrimidine bases (cytosine, thymine, uracil) of the nucleic acids (Sec. 21-14):

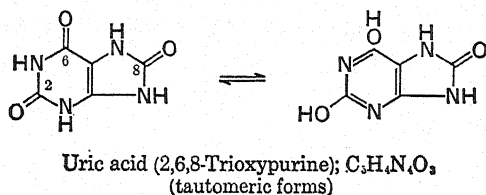
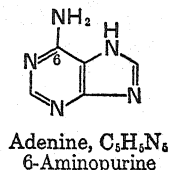
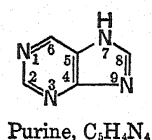


Pyrimidine, C₄H₄N₂
1,3-Diazine



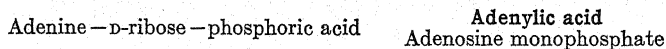
Cytosine, C₄H₅N₃O

Purine, a synthetic base, is the structural parent of uric acid, caffeine and related alkaloids (Sec. 26-15), and of adenine and guanine, the purine bases of the nucleic acids.



Uric acid is a dicyclic ureide related in structure to the barbiturates (Sec. 19-14). Two of its hydrogen atoms are acidic, and it forms both acid and normal salts, urates. It is a small but rather constant component of human blood and urine; birds and reptiles excrete most of their food nitrogen as uric acid, which is abundant in their solid excreta.

Adenine occurs in the nucleotide adenylic acid, in which it is joined at its 9 position with *D*-ribose:



Adenylic acid is one of three nucleotides (Sec. 21-14) which occur *as such* in animal tissues—that is, otherwise than as components of nucleic acids. The compound consisting of adenine joined with ribose (a nucleoside), which remains when the phosphoric acid group is hydrolyzed off, is called *adenosine*. The role of adenosine phosphates in fermentation and metabolism is referred to in Section 27-9.

PLANT ALKALOIDS

26-13 Most of the remedies used by primitive peoples have been roots or bark or leaves which seemed to have curative properties. The earlier scientists recognized that the effective action was due to some undetermined “active principle,” probably present in small amounts. The first of these to be isolated was *morphine*, a white crystalline base, extracted from opium in 1806 by Serturmer, an apothecary of Hanover. Since then, something like two hundred others, many having powerful pharmacologic action, have been separated from various plants. Since

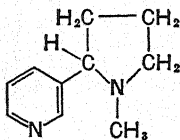
these compounds are bases and in this respect resemble the alkalies, they came to be known as *alkaloids*. At present, tablets containing accurately weighed quantities of pure alkaloid salts have almost entirely replaced preparations of crude drugs as medicinal agents.

Properties. Most alkaloids are colorless crystalline solids, though a few (*e.g.*, nicotine and coniine) are yellow liquids. Nearly all are optically active and have a bitter taste. Alkaloids are generally quite insoluble in water but dissolve freely in chloroform and ether. They contain one or more nitrogen atoms, to which they owe their property as bases. Their salts with the simple inorganic acids are usually quite soluble in water, and it is in this form that they are almost always used in medicine, *e.g.*, quinine sulfate, cocaine hydrochloride, codeine phosphate, strychnine nitrate. The alkaloids also form *insoluble* complex salts with many chemicals such as tannic, picric, phosphomolybdic, phosphotungstic, and chloroplatinic acids and potassium mercuric iodide. These are commonly known as the *general alkaloidal reagents*, and are used in precipitation tests to detect the presence of alkaloids.

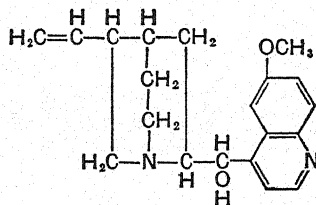
26-14 Structure. Eighty years after the first alkaloid was isolated, Ladenburg succeeded (1886) in synthesizing coniine, one of the simplest of them. Coniine, $C_8H_{17}N$, is 2-propylpiperidine. Since then the chemical structures of nearly all the others have been established. Many have been synthesized, but not by processes that can be industrialized; plants still remain the practical sources. The results of this work show that the nitrogen atoms in nearly all alkaloids are firmly fixed in the molecules as members of stable heterocyclic rings. Depending on the nature of these rings, the alkaloids are usually classified as derivatives of pyridine, pyrrolidine, quinoline, isoquinoline, and purine. Some examples follow.

26-15 Representative alkaloids include the following, the names and uses of which are more or less familiar to the general public.

Nicotine, a very poisonous oil found in the tobacco plant, contains a pyridine and a pyrrolidine—reduced pyrrole—nucleus. Such reduced heterocyclic nuclei are usually the ones which produce the strongest



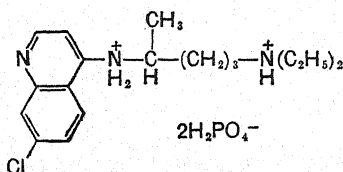
Nicotine, $C_{10}H_{14}N_2$



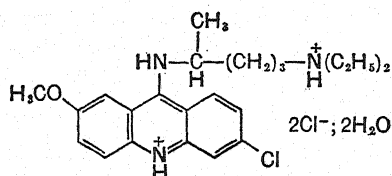
Quinine, $C_{20}H_{24}N_2O_2$
m.p. 175° ; $(\alpha)_D = -158^\circ$

pharmacological effects; they also contribute most to the basic properties of alkaloids in which they occur. Nicotine is extracted from tobacco stems and leaf trash by a distillation process and finds extensive use as an insecticide.

Quinine is obtained from the bark of the cinchona tree, which is native to the Andes in the region of Peru and is now cultivated extensively in the Netherlands East Indies. Extracts of the bark and leaves of this tree have been used for centuries as a cure for malaria. Quinine is specific against the parasite of malaria, and its use is the oldest application of chemotherapy (Sec. 14·16). Quinine has been synthesized within recent years but not by a method which permits its production. The Japanese occupation of the East Indies in 1942 cut off the major supply to the Western nations and led to a highly organized and intensive search for synthetic substitutes. This resulted in the factory production of several drugs which are regarded as even more effective than quinine. They include the following:

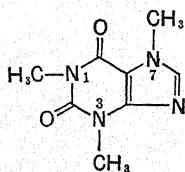


Chloroquine phosphate
 $C_{18}H_{26}ClN_3 \cdot 2H_3PO_4$
 (A quinoline derivative, like quinine)

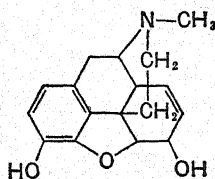


Quinacrine hydrochloride; Atabrine
 $C_{23}H_{30}ClN_3O \cdot 2HCl \cdot 2H_2O$
 (An acridine derivative)

Caffeine, a purine derivative, is the chief stimulant in coffee, tea, and a number of soft drinks. It is also used medicinally to stimulate the central nervous system. Theophylline and theobromine differ from caffeine in containing one less methyl group; both are important diuretics (increasing the secretion of urine).



Caffeine, $C_8H_{10}N_4O_2$

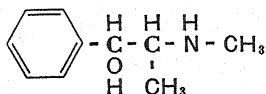


Morphine, $C_{17}H_{19}NO_2$
 (Formula for the free base, ordinarily
 used as the sulfate crystallizing with $5H_2O$)

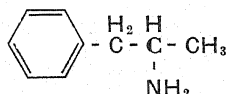
Morphine is the most important of a number of alkaloids obtained from opium, the dried excretion of the Oriental poppy. It was the first

alkaloid isolated (1806), but its complex structure was one of the last to be clarified. It contains a partially reduced phenanthrene ring and, if this be regarded as lying in the plane of the paper, a bridged six-membered ring containing a nitrogen atom, which should be pictured as extending upward toward the observer. One OH group is phenolic, and the other is that of a secondary alcohol. Morphine and some closely related derivatives, especially codeine, are invaluable analgesics—that is, drugs which relieve pain without producing loss of consciousness. All of them, however, are dangerously habit-forming. The search for equally effective synthetic analgesics which lack the habit-forming tendency has been long and arduous but not yet too successful.

Ephedrine is an organic base contained in the dried Chinese plant called Ma huang. This has been used medicinally for centuries. Ephedrine is one of the few alkaloids which does not contain a heterocyclic ring; it is best described as a phenylalkyl amine. The natural form is levorotatory.



Ephedrine, $\text{C}_{10}\text{H}_{15}\text{NO}$



Amphetamine, $\text{C}_9\text{H}_{13}\text{N}$
(generally used as the sulfate, which is also called benzedrine sulfate)

Ephedrine contracts the blood vessels, causes a prolonged rise in blood pressure, and has other properties similar to these of the hormone epinephrine, which it also resembles in structure. It is produced by chemical synthesis, as is also the related *amphetamine* which produces similar local effects.

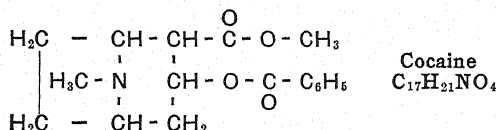
26-16 Synthetic Substitutes. Any plant containing one alkaloid is very apt to contain several; no less than 20 are present in opium. Hence the substitution of pure alkaloid salts for crude drugs was a great advantage, aside from the more accurate dosage, in making it possible to secure the action of one compound without the complicating effects of others. But even with pure alkaloids the desired action is often accompanied by objectionable secondary effects such as a tendency toward addiction.

The first attempts to modify favorably the action of the natural alkaloids were along the line of converting them into simple derivatives. Thus, the two hydroxyl groups of morphine were alkylated and acylated by standard methods. *Codeine*, the monomethyl ether of the phenolic hydroxyl, proved to be the most useful; it is not so powerful an analgesic as morphine but is less habit-forming than any related compound. On the other hand *heroin*, diacetyl morphine, proved to be even more habit-forming than the parent alkaloid.

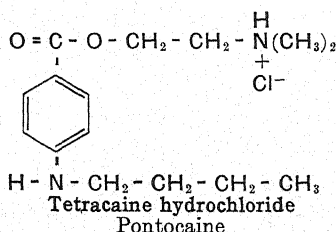
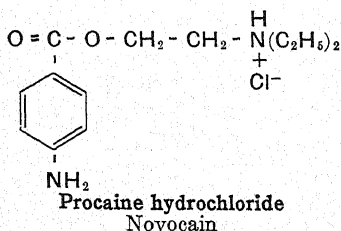
The second line of endeavor started with the hypothesis that the desired

action of the alkaloid is due to some specific structural unit in the molecule. This suggested the possibility of synthesizing a new compound having this essential structure but lacking the groups responsible for the objectionable secondary effects. Einhorn's work on cocaine substitutes is of special interest because it was the first systematic and successful effort.

Cocaine is a useful local anesthetic through its action in temporarily paralyzing the sensory nerve endings of the region to which it is applied; but, when absorbed, it stimulates and then paralyzes various parts of the central nervous system. It was known to have the following structural formula:



Seeking the effective part of this molecule, Einhorn and his associates prepared many simpler but related compounds and compared them with respect to anesthetic action and side effects. It gradually became evident that the five-membered pyrrolidine ring of cocaine has no influence on local anesthesia; the six-membered piperidine ring was found to assist, but carried with it the toxic properties of cocaine. On the positive side, it was observed that all the really effective compounds are bases and that all are esters. Finally, it developed that the highest activity is found in esters of *p*-aminobenzoic acid which also contain a dialkylamino group. *Procaine*, introduced by Einhorn in 1906 as *Novocain*, proved to be substantially as effective as cocaine and practically free from its aftereffects including habit formation. It has almost entirely replaced cocaine in medical practice. Some closely related synthetic compounds are used for special purposes, *e.g.*, *pontocaine*, for surface anesthesia in the eye, nose, and throat.



Ethyl *p*-aminobenzoate (benzocaine), which is substantially insoluble, is used in dusting painful wounds.

The plan which led to novocain set the pattern for many subsequent

research programs which have resulted in important developments in the field of synthetic medicinals. That such developments have not been even more numerous is largely because of the difficulties involved in correlating pharmacological activity with chemical structure. There exists no instrument for quantitative measurements comparable to the spectrophotometer in the field of color. In general, the useful products of synthesis have to be differentiated from the many others by a long and slow process of animal experimentation before they can be tried on man. Again, there is the great complexity of all living organisms—a complexity which makes it all but impossible to attain conditions under which just one factor at a time can be varied.

CHAPTER 27

ORGANIC CHEMISTRY AND LIFE

What we now call organic chemistry began as the study of compounds that occur in the bodies of living or *organized* plants and animals. Within a generation after Wöhler's synthesis of urea in 1828, the paralyzing theory of "vital force" had been displaced. Since then, man has duplicated most natural products in laboratories and often in factories and, in addition, has synthesized other organic compounds in almost infinite variety.

The fact remains, however, that man himself is a living organism and that—whatever be the ultimate secret—the processes upon which life depends involve a wide variety of organic reactions within the body. The fact remains also that man is still highly dependent upon reactions taking place in other living organisms. Plants and animals still furnish all the proteins, carbohydrates, and fats with which he sustains his body and most of the materials—cotton, wool, leather—with which he clothes it.

Biochemistry, which embraces all the reactions taking place in living organisms, is a very large body of knowledge with its own extensive literature and special methods of research. Even when restricted to the human animal the known facts and accepted theories defy any approach to an adequate summary of reasonable length. Yet a text or a course in organic chemistry is something less than "general" if biochemical relations are entirely neglected. Hence this final chapter which, in the nature of the case, must be illustrative rather than comprehensive.

27-1 The Need for Food. Living matter differs from lifeless in such distinctive properties as the ability to move, to grow, to reproduce, and—in warm-blooded animals—to maintain body temperatures above their surroundings. These functions involve the continuous expenditure of energy and the constant construction and reconstruction of living tissues. A continuous supply of *food* is necessary to provide the energy and the structural materials.

The major components of human food are: *carbohydrates*, mainly as starch from sources such as cereal products and potatoes; *fats* and fatty oils, from butter, meat fats, salad oils, etc; and *proteins* derived from lean meat, fish, eggs, milk, and to some extent from plant products. An adequate diet must contain, in addition, minute but indispensable

quantities of vitamins (Sec. 27-11), small amounts of various inorganic salts, and large quantities of water. The salts and water are necessary to provide the physical environment suitable for living cells. Water assists also in the regulation of body temperature and in the elimination of waste products.

27-2 Digestion. Most of the food which enters the human mouth consists of complex, insoluble molecules of starches, proteins, and fats. The over-all effect of the changes which occur in the digestive tract is the conversion of these food components into products which are (1) *soluble* in dilute salt solutions—the body fluids; (2) simple enough *physically* to diffuse through the intestinal wall and thus be absorbed into the living body proper; and (3) simple enough *chemically* to be utilizable by the living cells to which they are carried by the blood or lymph.

The chemical reactions of digestion consist in a series of hydrolytic cleavages catalyzed by specific enzymes (Sec. 27-6). *Starch* is hydrolyzed progressively, beginning in the mouth with the aid of the salivary enzyme ptyalin, through dextrins and maltose, to glucose (Sec. 18-30). *Proteins* are hydrolyzed, beginning in the stomach with the aid of pepsin secreted by its walls, via proteoses, peptones, and peptides, to a mixture of α -amino acids (Sec. 21-9). Ordinary *fats and fatty oils* are not affected by the saliva or gastric juice; they are emulsified in the upper intestine with the aid of soaplike salts furnished by the bile, and hydrolyzed to glycerol and fat acids (Sec. 16-19) with the aid of the enzyme steapsin from the pancreas. This secretion of the pancreas¹ also contains an amylase and a protease (trypsin), which aid in completing the digestion of starch and protein, respectively.

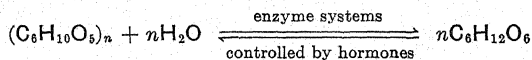
27-3 Metabolism is the sum of the chemical changes which occur between the absorption of digestion products and the excretion of their component atoms from the body—carbon as carbon dioxide, hydrogen as water, and nitrogen for the most part as urea. It includes all the reactions involved in the performance of vital functions, including the building up and breaking down of protoplasm and the disposal of worn and displaced parts. Knowledge of this complicated field has been greatly increased in recent years through feeding compounds which contain isotopic atoms of one or more of the elements C, H, N, O, or P, and determining what becomes of these "labeled" atoms. Thus the

¹ Soon after the partly digested food passes from the stomach into the small intestine, it is mixed with bile from the gall bladder and the "pancreatic juice," which are discharged into the intestine through a common duct. This external secretion of the pancreas, containing the digestive enzymes which it manufactures, must not be confused with the *internal* secretion of insulin (Sec. 27-24) which passes directly into the blood.

exchange between the food amino acids circulating in the blood and those which form parts of living protein tissues has been followed by feeding amino acids containing isotopic carbon and nitrogen atoms. This exchange was found to be unexpectedly rapid and extensive.

The essential function of the food proteins is to supply those amino acids which are indispensable for the construction and maintenance of the tissue proteins and for other necessary syntheses (Sec. 27·5). Amino acids in excess of the requirement (and those released by protein tissues) are promptly *deaminized*—that is, they are cleaved to ammonia and a nonnitrogenous residue, usually a keto acid. Most of the ammonia is converted to urea in the liver and excreted as such in the urine. The nonnitrogenous residues are oxidized, through sequences of reactions, to carbon dioxide and water; some of them, *e.g.*, that from alanine, may be first converted into glucose. It should be emphasized that the healthy adult cannot store protein under normal circumstances. His measured intake and output of combined nitrogen are equal—a condition described as being in *nitrogen equilibrium*. A plus nitrogen balance, showing protein storage, is observed only during conditions such as growth, pregnancy, recovery from a wasting illness, or *intense* muscular activity (muscle building).

Most of the glucose (and any fructose and galactose) entering the blood stream from the digestive tract is converted into glycogen (Sec. 18·31) which is stored temporarily in the liver and muscular tissues. This capacity for carbohydrate storage in animals is strictly limited; occasionally a man may store as much as a pound of glycogen, but this is rare. Liver glycogen serves mainly as a reservoir for maintaining the low, normal concentration of glucose in the blood; when the blood-sugar level tends to rise, following a meal, glycogen is stored; when it begins to fall, through oxidation of glucose, glycogen is hydrolyzed:



Muscle glycogen performs the additional function of serving in the path of carbohydrate oxidation (Sec. 27·16). Excess carbohydrate can be given more permanent storage through conversion to fat. This is applied in the heavy feeding of grain to hogs and cattle being “fatted” for marketing; its operation is observed also in the bodies of most people who eat heavily and exercise little. The details of the conversion of glucose into fat are still obscure.

Glycerol and fat acids produced in digestion of the food are quickly recombined to fats which enter the lymphatic system and pass thence into the blood. They are stored, in part, to replace or augment previous

deposits of tissue lipides. The visible depot fats—such as the subcutaneous layer, an inch or more thick, found on a slice of ham—are composed chiefly of mixed glycerides (Sec. 16-17) in which the proportion of saturated fatty acids is relatively high. Those parts of the body which are biologically more active—the brain, nervous system, spinal cord, etc.—contain much higher proportions of highly unsaturated fats and of phosphatides and sterols. In part, the food fats are oxidized to carbon dioxide and water with the release of energy. Details of this and other phases of metabolism may be found in standard texts on biochemistry.

27-4 Calorific Values of Food. When one mole of glucose, 180 grams, is oxidized completely to carbon dioxide and water, the heat evolved is 673 kcal—the same, whether this occurs in a bomb calorimeter or in the animal body. This equals 3.74 kcal per gram of $C_6H_{12}O_6$ or 4.15 per gram of original food starch, $(C_6H_{10}O_5)_n$. In dietary calculations carbohydrate food is figured at the rounded average value of 4 kcal per gram. The average fat or fatty oil gives 9.4 to 9.5 kcal per gram in the calorimeter, which is reduced to 9 kcal in dietary work to allow for incomplete absorption. The reasons for this large difference in the food values of carbohydrate and fat have been indicated (Sec. 11-17) and should be reviewed. The practical dietary value for protein food is 4 kcal per gram although average protein gives 5.7 kcal when burned in a calorimeter (nitrogen converted to N_2). The difference lies in the higher energy content of urea (end product in the body) as compared with elementary nitrogen.

27-5 Food Requirements. The food must supply energy equivalent to that which the body expends in muscular activity¹ and radiates as heat. This amounts to 2500 to 3000 kcal per day for the average male adult and more for those who perform heavy physical labor. Such an amount is supplied, for example, by a diet which contains on a dry basis:

Protein.....	80 grams	$\times 4 =$	320 kcal
Fats and fatty oils.....	100 grams	$\times 9 =$	900 kcal
Carbohydrate.....	420 grams	$\times 4 =$	1680 kcal
	1.3 pounds		2900 kcal

Distribution. If a diet is adequate over-all, the relative proportions of carbohydrate and fat may be varied within wide limits. Carbohydrate is generally cheaper and usually predominates; but Eskimos replace it very largely by fat. Protein, on the other hand, exercises a specific function which forbids reduction below a certain minimum. That function is to supply the amino acids which the body is unable to synthesize—

¹ The major part of the work performed by the body is internal—that is, for purposes such as pumping the blood and moving the lungs in breathing.

the *indispensable* or *essential* amino acids. These are necessary both for the construction of tissue proteins and for the synthesis of special proteins such as enzymes and certain hormones. Insulin, for example, contains at least five of these indispensable acids—threonine, arginine, lysine, leucine or isoleucine, and histidine (Table 21·2). The need for these particular molecules is so specific that in some instances the natural compound cannot be replaced even by its mirror-image isomer. About 70 grams of protein food per day is considered a safe minimum for an adult if the diet includes a variety of proteins.

ENZYMES

Some of the reactions which occur in digestion duplicate industrial processes which yield the same products. The huge soap-and-glycerol industry is based on the hydrolysis of fats and fatty oils by lye and steam. Corn sugar and corn syrup are manufactured by hydrolyzing starch to glucose with steam and acid. A living animal accomplishes these same ends without any such drastic conditions; the reactions proceed with satisfactory speed at body temperature, below 40°C, and within the very narrow limits of acidity and alkalinity which living cells can tolerate.

This remarkable facility of living things to effect the chemical changes of digestion, and the much more complicated ones which follow in metabolism, depends upon the presence and activities of enzymes.

27·6 Enzymes are organic catalysts produced by living cells. Under all normal conditions plant and animal organisms synthesize within themselves whatever enzymes they require; they are not components of food. All enzymes which have been obtained in crystalline form and, presumably, as pure chemical compounds, are proteins, *e.g.*, pepsin, trypsin, urease, catalaze. The others show definite protein characteristics. They give many protein precipitation reactions and color tests, and they dialyze slowly if at all. There is an *optimum temperature* at which any enzyme acts most effectively; this is close to the normal body temperature for most of those found in warm-blooded animals. Activity is reduced by cooling but can be restored by returning to the optimum temperature. At higher temperatures, usually not over 70°C in the presence of water, activity is destroyed irreversibly—a phenomenon which is doubtless associated with the denaturation and coagulation of proteins. For each enzyme there is a narrow pH range within which it acts most effectively, *e.g.*, 1.2 to 1.6 for pepsin and 7.5 to 8.3 for trypsin; outside it, activity is sharply decreased or the enzyme may be destroyed rapidly. This optimum pH is usually close to, though not identical with, the isoelectric point.

27·7 Specificity. The activities of enzymes are governed by the same

general laws that apply to other catalytic agents: they are able to accelerate or initiate reactions in which they themselves are not consumed; small amounts are capable of changing a large but not an indefinite quantity of another substance; they catalyze both the forward and reverse processes of reversible reactions; their activity may be inhibited by combination with reaction products or by-products.

But there are important differences, aside from origin and composition, between enzymes and common inorganic catalysts such as platinum black. Most striking is the remarkable *specificity* of enzyme action. Colloidal platinum catalyzes many different reactions between the most diverse substances. On the contrary, the activity of any enzyme is limited to one substance, commonly known as its *substrate*, or to a few compounds of closely related structure; activity is likewise limited to catalyzing reactions of a particular type, such as oxidation or hydrolysis, but not both. For example, pancreatic lipase readily *hydrolyzes glycerides*, but has no influence upon the hydrolysis of either starch or protein and does not catalyze any reaction of glycerides *except* hydrolysis. A still higher degree of specificity is observed in the selective action of enzymes on optical isomers. Only the natural, *D* forms of glucose and fructose are fermentable by the zymase system of enzymes contained in ordinary yeasts; the synthetic, mirror-image isomers of the *L* series are not affected. This high specificity makes it possible to distinguish between α - and β -glucosides by the use of enzymes (cf. Sec. 18·15).

These and many similar observations show that enzymotic activity depends intimately upon definite agreements in molecular structures. Emil Fischer expressed this long ago in his famous statement that "the configuration of an enzyme and that of its substrate must correspond as a key does to a lock." Unfortunately, we are still not too clear as to just how the key operates the lock.

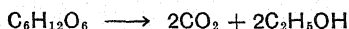
27·8 Terminology. The systematic name of an enzyme is formed by adding *-ase* to the name of its substrate, *e.g.*, one which hydrolyzes starch (*L.*, *amylum*) is an amylase, one which hydrolyzes proteins is a protease, etc. Often *-ase* is added to the name of the type of reaction catalyzed; thus enzymes which catalyze dehydrogenations and phosphorylations (esterification with phosphoric acid) are called dehydrogenases and phosphorylases, respectively. Some of the enzymes first recognized are still generally known by the nonsystematic names given them originally; *e.g.* the "gastric protease" extracted industrially from the stomach lining of calves is *pepsin*.

Coenzymes. Many enzymes can be separated by dialysis into a non-diffusible protein, which is deactivated by heating, and a diffusible, heat-stable *coenzyme*. The latter is some relatively simple organic molecule

such as adenosine triphosphate or thiamine pyrophosphate (Sec. 27.9). Neither component is active alone, but together they form an effective enzyme-coenzyme system.¹ The protein part is specific to a particular substrate; a coenzyme may be able to function in many different systems. It is generally assumed that, as they occur in nature, the coenzyme is loosely combined with the protein, probably as the prosthetic group of a conjugated protein (Sec. 21.13).

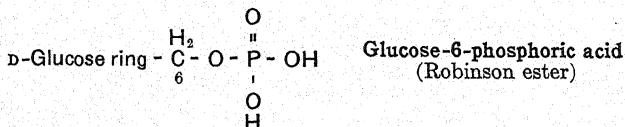
27.9 Alcoholic fermentation, a biochemical process older than recorded history, involves the catalytic action of many enzyme-coenzyme systems. Pasteur's classical researches, beginning in 1857, threw much light on the confused subject but left him with the belief that "alcoholic fermentation is an act correlated with the life and organization of yeast cells. . . . The chemical act of fermentation is . . . correlative with a vital act, commencing and ceasing with the latter." Buchner, in 1897, disproved this. He ground yeast thoroughly with sharp sand to break up the cells, used high pressure to squeeze out yeast juice, and filtered the latter through porous porcelain to remove any trace of living matter. The filtrate was still able to excite violent fermentation in sugar solutions. Buchner ascribed this activity to the presence of a soluble enzyme, which he called *zymase*, produced by the living cells but capable of acting without, as he said, "so complicated an apparatus as a yeast cell."

The *zymase* which Buchner considered *an* enzyme is now recognized as a complex of enzymes, containing many different enzyme-coenzyme systems which catalyze successive steps in alcoholic fermentation. The over-all equation for the formation of alcohol from glucose



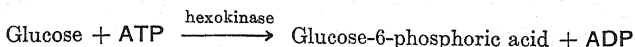
is not strictly quantitative. Glycerol is always formed in appreciable amounts, and other organic compounds can be detected. Attempts to explain the origin of these by-products led to the gradual unraveling of the fermentation process, which is now known to consist of some 12 consecutive reactions, each catalyzed by a component of "*zymase*." A few of these are described below in order to illustrate the high complexity of the process.

The first step in the alcoholic fermentation of glucose is its esterification by phosphoric acid at the C⁶ hydroxyl, forming

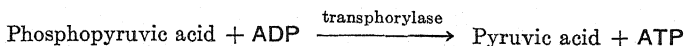


¹ Biochemists commonly call the system a *holoenzyme* (from Gr., *holos*, complete, entire) and the protein part the *apoenzyme*.

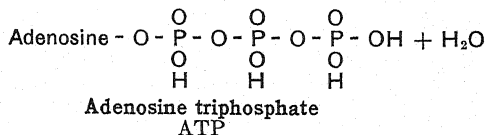
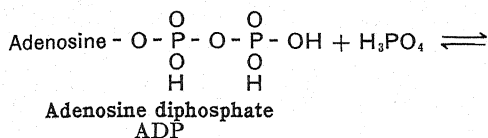
This reaction occurs with the aid of a protein enzyme, hexokinase, and its coenzyme adenosine triphosphate, ATP:



The other reaction product is adenosine diphosphate, ADP. At a later stage in the process of fermentation ATP is regenerated, *e.g.*,

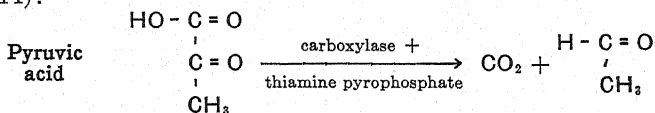


The adenosine phosphates are related as follows:



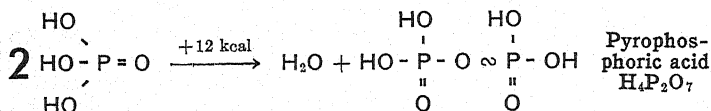
The structures of adenosine and of the nucleotide adenosine monophosphate (AMP, adenylic acid) were indicated in Section 26-12.

The last two stages of alcoholic fermentation are the decarboxylation of pyruvic acid to acetaldehyde and reduction of the latter to ethyl alcohol. The pyruvic acid reaction is catalyzed by carboxylase, which requires as coenzyme the pyrophosphate ester of vitamin B₁ (thiamine, Sec. 27-14):



Role of Phosphates. Pasteur recognized that phosphates must be supplied to yeast cultures for normal growth and activity. We now know that the process of fermentation involves many reactions in which phosphoric acid is added to and removed from intermediate products by reactions analogous to those indicated above. This is true likewise in the intermediate metabolism of carbohydrate in the animal body.

The esterification of an alcohol by phosphoric acid is a mildly endothermic reaction absorbing about 3 kcal per mole. But formation of the anhydride type of linkage between two molecules of H₃PO₄, as found in pyrophosphoric acid and in ATP and in ADP, absorbs about 12 kcal per mole for each such bond:



These *high-energy* phosphate bonds are often indicated by the symbol \approx . It is believed that their formation in muscular tissues serves as an important means for the temporary storage of energy in a form quickly available for use.

27-10 Enzymes in Industry. Yeasts, molds, and bacteria are used to bring about various chemical transformations on an industrial scale. Most and possibly all such changes depend upon the catalytic activities of enzymes secreted by the microorganism rather than upon some direct action of its living cells. The manufacture of ethyl alcohol and of butanol and acetone by fermentation processes have been described already. Vinegar is produced from dilute ethyl alcohol with the aid of *Bacterium aceti*, and citric acid is manufactured in large quantities from molasses, using a special strain of *Aspergillus niger*. The souring of milk, the manufacture of cheese, sewage disposal, and the fixation of atmospheric nitrogen in the root nodules of leguminous plants are other processes which involve the action of microorganisms or enzymes which they secrete. Proteolytic enzymes are used in manufacturing leather to dissolve out certain of the hide components, leaving the fibrous collagen which is later combined with tannins.

VITAMINS

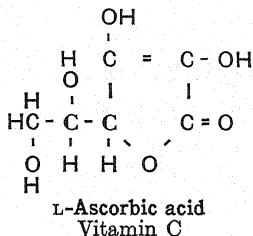
27-11 Vitamins are compounds which cannot be synthesized in the animal body but which are required in small amounts for its proper functioning. A varied diet normally supplies them in adequate amounts. Many and possibly all of them produce their effects by serving as components of essential coenzymes (Sec. 27-16).

The existence of vitamins was first indicated by observations such as the following: The disease known as *scurvy* was widely prevalent among seamen in the days of sailing vessels when fresh foods were not available; long before the existence of vitamins was suspected, this disease was practically eliminated by including in the ration such substances as lime juice and cabbage. Again, in the Orient, *beriberi* was widely prevalent among the poorer classes whose food consisted chiefly of *polished* rice, *i.e.*, grains from which the outer brown coating had been removed. Until about 1884, this disease was the scourge of the Japanese navy, where the ration consisted of fish and polished rice. In that year an observant official made comparisons with the food of the British navy, where the disease was unknown, and, by broadening the diet, quickly reduced its

occurrence among the Japanese. Scurvy and beriberi became known as *deficiency* diseases since it was obvious that they were due to the lack of some unknown but necessary substances that should be supplied in the food.

Gradually, one by one, many of these unknown substances—which we now call vitamins—have been isolated and their structures and specific functions determined. Most of them have been synthesized, and a few are manufactured on an impressive scale¹ by chemical syntheses. Before their structures were determined, the first vitamins recognized were designated by letters of the alphabet (vitamins A, B, C, etc.). These terms are being replaced gradually by more definitive names, *e.g.*, ascorbic acid instead of vitamin C. The examples given below and the formula for vitamin A (Sec. 4-13) will serve to illustrate the wide diversity in their chemical structures. No attempt will be made here to list all the known vitamins.

27-12 Ascorbic acid is the antiscorbutic or scurvy-preventing substance present in citrus fruits and fresh vegetables. It is manufactured by the catalytic hydrogenation of glucose to D-sorbitol (Sec. 16-15), which is converted via three intermediate steps into ascorbic acid:



Ascorbic acid is much more highly ionized than carboxylic acids such as acetic and forms a well-defined monosodium salt. Acidity is due to the enediol system, which also makes it a strong reducing agent. Since it is readily oxidized by air, especially when in hot solutions, much of the ascorbic acid present in fresh vegetables such as beans and cabbage is usually destroyed in canning or cooking.

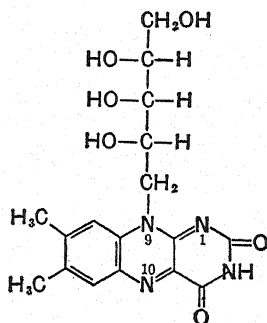
The minimum daily requirement of 30 mg of ascorbic acid for an adult is considerably larger than for most vitamins. This is normally supplied by a diet which includes fresh fruits and uncooked leafy vegetables. Deficiencies can be made good by the synthetic compound, which wholesales at about $2\frac{1}{2}$ cents a gram.

27-13 Vitamin B Complex. The discovery that beriberi could be

¹ The production of vitamins by chemical synthesis in the United States in 1951 approached 4.5 million pounds with a wholesale value around 90 million dollars. Niacin, ascorbic acid, thiamine, and riboflavin are produced in the largest amounts.

of the carboxylase enzyme system. A deficiency is indicated rather promptly by nervous symptoms; severe and prolonged deficiency gives rise to beriberi. The thiamine requirement depends upon the total metabolism. The minimum is about 0.03 mg per 100 kcal or about 1 mg per day for 3000 kcal; the optimum is 1.5 to 2.5 mg per day. Synthetic thiamine is used, among other purposes, for addition to bread—to replace the natural thiamine of the outer layer of wheat, which is removed in modern milling in order to produce the white flour which the public demands!

27-15 Riboflavin is a water-soluble, yellow-green pigment first recognized in milk whey and later isolated from yeast, liver, egg white, etc. Kuhn obtained 0.1 gram of it from the dried whites of 33,000 eggs. It is now manufactured by chemical synthesis, in amounts comparable to thiamine, and is used for nutritional and therapeutic purposes. These include addition to bread and to poultry foods. Riboflavin promotes growth in young animals and is necessary in order to prevent a number of disorders. The daily human requirement is of the order of 2 to 3 mg. The chemical formula is



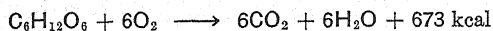
Riboflavin, $C_{17}H_{20}N_4O_6$
Lactoflavin; Vitamin B_2
(Vitamin G)

The carbohydrate fragment of the molecule is derived from D-ribose. The formula shows the oxidized molecule; on reduction two atoms of hydrogen are added at positions 1 and 10.

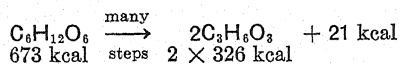
27-16 Vitamins as Coenzymes; Biological Oxidation. Many vitamins are known to produce their observed effects by serving as components of essential enzyme systems. This role of the B vitamins in biological oxidation has been established most convincingly.

Animals obtain substantially all their energy through the biological oxidation of substances derived from the food. These include the fat acids and glycerol, the deaminized residues of amino acids, and—most

important of all—glycogen and glucose. We will consider only the metabolism of glucose, which is summarized by the over-all equation



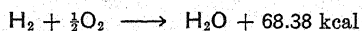
The earlier stages of this process involve the same sequence of about 10 reactions as in alcoholic fermentation. These are catalyzed by specific enzyme systems, similar to those of zymase, which are present in muscle extracts. Metabolism and fermentation part company with the formation of pyruvic acid, $\text{CH}_3\text{CO}\cdot\text{COOH}$. Muscle does not contain the carboxylase which with yeast gives acetaldehyde. Instead, working muscle reduces pyruvic to lactic acid, $\text{CH}_3\text{CHOH}\cdot\text{COOH}$. The over-all effect to this point releases very little energy:¹



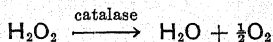
The important energy release occurs in the subsequent changes, through which lactic and pyruvic acids are finally oxidized to carbon dioxide and water. This again is a complicated series of step-by-step reactions catalyzed by specific enzyme systems.

Biological oxidation rarely if ever involves the addition of elementary oxygen to an organic molecule. The initial step is nearly always a *dehydrogenation* (cf. Sec. 10-2, paragraph 3). The oxygen atoms not in the original molecule but appearing in the end product, CO_2 , enter through *addition of water* at one or more stages in the process. We have seen already how, for example, water can add to $\text{C}=\text{C}$ and $\text{C}=\text{O}$ bonds.

In a biological dehydrogenation, hydrogen atoms are not removed as protons or as free hydrogen. They are taken up by a mediator—the oxidized form of a coenzyme, which is thereby reduced. The coenzyme is present in very small amounts, and dehydrogenation would quickly cease if it were not coupled with another reaction in which hydrogen is passed on to a second hydrogen acceptor and the coenzyme converted back into its oxidized state. Such a chain of reactions may proceed through several mediators until, at last, *hydrogen is accepted by oxygen*. This may be either to form water directly

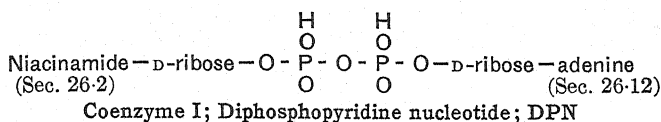


or to form hydrogen peroxide. The latter is quickly decomposed by catalase, an enzyme which appears to be present in all living cells:

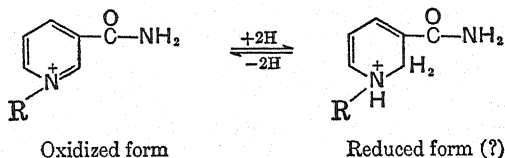


¹ It is interesting to note that the net energy decrease in alcoholic fermentation is likewise very small; the two moles of $\text{C}_2\text{H}_5\text{OH}$ formed from a mole of glucose yield 2×327.6 kcal when burned.

The outstanding function of the B vitamins is in coenzymes which act as mediators or acceptors in biological dehydrogenations. Niacin (as niacinamide) acts in this way when combined in the nucleotide:



Niacinamide functions in like manner in Coenzyme II, a compound of similar structure containing a third phosphoric acid group (in a position not definitely known). These coenzymes are able to conjugate with many different protein enzymes to form systems which are effective in catalyzing specific dehydrogenations. The essential reaction appears to be that of the pyridine nucleus of niacinamide, which is reduced and oxidized reversibly, as follows:



The ring nitrogen atom in the oxidized molecule is in the condition of a quaternary ammonium ion, which forms an inner salt with one of the ionizable phosphoric acid groups contained in **R** of the coenzyme; the structure of the reduced, dihydro compound is not yet definitely established.

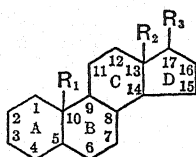
The reduced form of niacinamide, in Coenzyme I or II, passes on two hydrogen atoms to another mediator. Frequently this is a riboflavin coenzyme (made up of riboflavin, phosphoric acid, D-ribose, and adenine, joined in a manner similar to Coenzyme I, above). The riboflavin group is able to accept hydrogen at its 1 and 10 positions and then pass them on.

Other B vitamins are known to act in a similar manner. This is probably true also of readily oxidizable ascorbic acid though the details are not clear.

27-17 Vitamin D regulates the metabolism of calcium and phosphorus. It is necessary in order to prevent infantile *rickets*—a disease which involves the malformation of bone—and certain other conditions both in children and adults. Fish oils, such as halibut-liver oil, are the richest natural sources of vitamin D. (These are also important sources of vitamin A.) The inclusion of these oils in the diet was recognized as a preventive and cure for rickets before vitamin D was discovered. It was known, also, that exposure of the skin to the ultraviolet radiation of

direct sunlight was beneficial in the treatment of rickets; and it developed that certain foods which lack the antirachitic property acquire it when exposed to ultraviolet rays. Ultimately, two antirachitic substances were isolated and their structures determined (Sec. 27·20). Both are sterols.

27·18 Sterols and Steroids. The term sterol, meaning solid alcohol, is applied to certain complex alicyclic alcohols which occur widely in plant and animal tissues. The more general class of compounds to which they belong is called the *steroids*. All steroids contain the carbon framework represented by the ring system:



Rings A, B, and C constitute a reduced phenanthrene nucleus, to which ring D is fused. R_1 and R_2 are almost invariably methyl groups. R_3 varies widely; it may be a hydrocarbon radical, such as C_8H_{17} in cholesterol, or it may be as simple as a hydroxyl group.

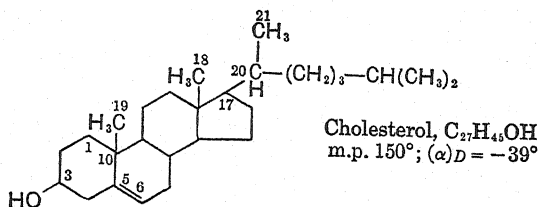
The steroid ring system occurs in a remarkable variety of biologically important compounds. These include the D vitamins, ergosterol, cholesterol, the bile acids, and many hormones (also the cardiac glycosides and the toad poisons, which will not be considered here).

27·19 Cholesterol is the principal animal sterol and seems to occur in all animal cells. It was first isolated from gallstones and derives its name from its presence in bile (Gr. *chole*, bile). It is especially abundant in brain and nervous tissue and is produced from the spinal cords of cattle.¹ Wool fat is another important occurrence. Cholesterol is insoluble in water but dissolves in fat solvents, from which it crystallizes in thin, transparent, colorless plates.

Cholesterol is a monohydric secondary alcohol and contains one double bond which can be detected by the addition of bromine. Its structure—which was established with the utmost difficulty—is shown by the formula²

¹ The fats are first saponified to soaps; cholesterol, being an alcohol, is unaffected by the treatment with alkali and can be extracted from the residue by ether, chloroform, or a similar solvent. The "nonsaponifiable residues" from all animal fats contain more or less cholesterol.

² In such conventional formulas for the steroids, each angle indicates a carbon atom with enough hydrogen atoms attached to complete its valence of four; for example, cholesterol has one hydrogen at 3, 6, and 17 and none at 5 (where four valence bonds are shown).



Cholesterol contains eight asymmetric carbon atoms, which indicates that it is one of 256 theoretically possible stereoisomers. Geometrical isomerism is also possible in this and other steroids (*e.g.*, the OH on C^3 might be either *cis* or *trans* to the CH_3 group on C^{10}). These facts are mentioned because they suggest the tremendous difficulties involved in the *total* synthesis of a specific steroid.¹ This explains why, up to the present at least, the production of D vitamins and steroid hormones must begin with some fairly abundant natural steroid such as cholesterol or cholic acid.

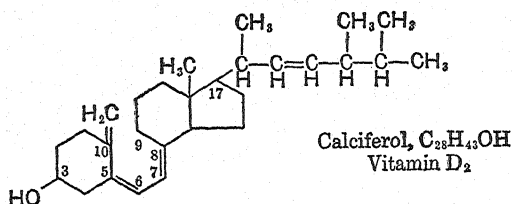
Cholic acid, $C_{23}H_{36}(OH)_3.COOH$, is the most abundant constituent of human and ox bile. It has no double bond, the OH groups are on C^3 , C^7 , and C^{12} , and the carboxyl group is in the side chain attached to C^{17} . It melts at $195^{\circ}C$ and is dextrorotatory, $(\alpha)_D = +37^{\circ}$. In *desoxycholic acid*, the OH group on C^7 is missing.

Cholic acid occurs in bile conjugated with an amino acid. This is glycine in glycocholic acid and taurine, $H_2N.CH_2.CH_2.SO_3H$, in taurocholic acid. The sodium salts of these conjugated acids (the "bile salts") are soaplike substances which assist digestion of the fatty foods by aiding in their emulsification and absorption.

27-20 Ergosterol; Calciferol. The most abundant plant sterol is ergosterol—so named because it was first isolated from ergot. Yeast is an important source. It is also found in animal tissues, including the skin. Ergosterol, $C_{28}H_{44}OH$, differs from cholesterol mainly in that it contains three double bonds instead of one and has one additional carbon atom in the C^{17} side chain.

The observation that sunlight was beneficial in the treatment of rickets led to the supposition that something in the skin was being converted into an antirachitic vitamin. Further investigation proved this "something" to be ergosterol, which is converted into calciferol, vitamin D_2 . The only chemical change involved is the opening of ring B, between C^9 and C^{10} , and the conversion of the C^{19} side chain from $-CH_3$ to $=CH_2$. Thus calciferol has the same molecular formula as ergosterol:

¹ One total synthesis was announced in May, 1951. The product contains the usual steroid four-ring system, three double bonds, and four asymmetric centers.



Calciferol is now manufactured and obtained in pure crystalline form by irradiating ergosterol with ultraviolet light or by bombarding it with electrons. Calciferol is dextrorotatory.

Vitamin D_3 , viosterol, $C_{27}H_{43}OH$, is produced in like manner from a cholesterol derivative, 7-dehydrocholesterol. It differs in structure from calciferol only in containing the saturated *eight*-carbon side chain of cholesterol at C^{17} . This appears to be the vitamin present in fish-liver oils. Both D_2 and D_3 have powerful antirachitic properties but are not equally effective in all species; *e.g.*, fish-liver oils and synthetic D_3 are preferred for poultry and calciferol, for man.

HORMONES

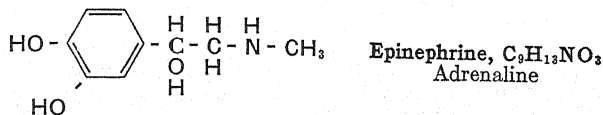
27.21 An outstanding characteristic of living things is the *coordination* of activities implied by the term *organism*. In this connection the roles of the mammalian brain and nervous system have long been recognized—and, formerly, were overestimated. It is now known that the coordination of many bodily activities is effected by specific chemical compounds transported by the blood. These substances are called *hormones* or chemical messengers.

Hormones are organic compounds synthesized in various organs, such as the thyroid and pituitary glands, adrenals, testes, and ovaries, and discharged in minute quantities *directly* into the blood or lymph. Once in the general circulation, they are carried to all parts of the body. They exert prompt and very powerful influences upon specific organs, probably through affecting enzyme systems. Hormones vary in structure between relatively simple compounds such as epinephrine to full-size proteins, *e.g.*, insulin.

Evidence of the existence of hormones was obtained by observations and experiments such as the following: It was known that the pancreas commences to discharge its digestive fluid, via the common bile duct, into the intestine *only* when the partially digested food arrives there from the stomach. It was also known that direct mechanical stimulation was impossible and that the coordination persisted after all nervous connections were severed. Bayliss and Starling (1902) inferred that the stimulus originated when the *acid* gastric contents came in contact with the intestinal wall. They further assumed that this caused the discharge into the blood of a substance which was carried to the pancreas and which excited it to activity. Proof was furnished by connecting the veins and arteries of two dogs to give a common circulation;

when dilute hydrochloric acid was placed in the intestine of one animal, the pancreas of *each* became active. The particular hormone responsible for this effect, known as *secretin*, has been isolated but its structure is still not clearly established.

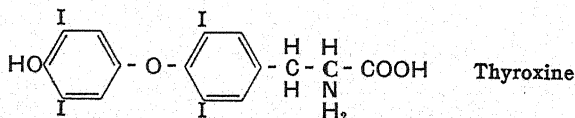
27-22 Epinephrine was the first hormone isolated and the first to be synthesized (1906). It is a catechol derivative and is produced from this phenol for medicinal use. The structural formula



shows the presence of one asymmetric carbon atom. The *levorotatory* natural form is said to have about fifteen times the pharmacological activity of its mirror-image isomer. Epinephrine excites the endings of sympathetic nerves, constricts arterioles, and produces a general rise in blood pressure and steadying of the heartbeat. It has also a powerful effect on carbohydrate metabolism, particularly in increasing the rate at which stored glycogen is converted into blood sugar. Its therapeutic uses include the relief of asthmatic attacks and the relief of surgical and some other forms of shock by increasing blood pressure. Epinephrine is quickly oxidized in the body, and its effects are therefore transient.

Epinephrine is produced naturally by the *medulla* or inner portion (cf. Sec. 27-26) of the small adrenal glands situated upon the kidneys. The rate at which it is discharged into the blood is influenced by the sympathetic nervous system and is stimulated powerfully by psychological factors.¹

27-23 Thyroxine is the active constituent of the major hormone of the thyroid gland. Through it this organ exerts its powerful control over the rate of *total* metabolism. A minute quantity of crystalline thyroxine was isolated from beef thyroids by E. C. Kendall,² who later worked up some tons of the dried glands to obtain enough for study. The compound was synthesized by Harington in 1926. Thyroxine is a derivative of tyrosine with the structure



¹ For example, Cannon showed that the sensations of fear and anger stimulate the secretion of epinephrine; this increases heart action, blood pressure, and glucose in the blood. Thus, the body is prepared for the extra muscular effort required for the *fight* and *flight* which are the instinctive responses to anger and fear.

² Cf. footnote page 552. Kendall states that crystalline thyroxine was first seen "on Christmas day, 1914."

The natural form is the *levo* isomer. Thyroxine exists in the thyroid gland as the prosthetic group of a conjugated protein, thyroglobulin. It appears also to be in some form of protein combination as it circulates in the blood. Various derangements due to inadequate development or malfunctioning of the thyroid gland have been treated successfully with thyroxine. An effect of too much thyroxine is observed in the overstimulation of metabolism associated with the enlarged thyroid of exophthalmic goiter.

27-24 Insulin. It has long been realized that the pancreas performs a necessary function other than the manufacture of the digestive enzymes that it secretes through a visible duct into the intestine. Complete removal of the organ quickly produces, aside from disturbance of digestion, loss of the ability to oxidize sugars and symptoms like those of advanced diabetes. Death follows shortly. These consequences can be avoided if a portion of the pancreas is left or if it is entirely removed but grafted back anywhere inside the abdominal cavity. Since the operation severs all nervous connections, it became apparent that the pancreas acts through a substance which it discharges into the blood.

In 1921, Macleod and Banting¹ were able to prepare an extract of the pancreas which, when injected into diabetic patients, powerfully stimulated the disturbed carbohydrate metabolism and relieved the other symptoms of the disease. The active hormone responsible for these effects they called *insulin* (on account of its occurrence in the so-called *islands* of Langerhans of the mammalian pancreas). Insulin has since been obtained in crystals believed to be pure. The crystals are those of a protein with a molecular weight of 35,000 to 40,000 and an isoelectric point of 5.35. The amino acid distribution in insulin is given in Table 21-2.

Diabetic patients are now treated and kept in good health for years by the regular hypodermic injection of standardized insulin preparations obtained from extracts of animal pancreas. Being a protein, and subject to hydrolysis by proteases of the digestive tract, it cannot be given by mouth. A slow, steady absorption is desirable in order to decrease the number of injections per day. This is secured by using a sparingly soluble combination of insulin with zinc and another protein (a histamine or a globulin); these complexes are able to maintain effective blood-sugar control for as long as 24 hours.

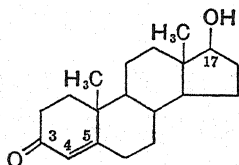
The effect of insulin in stimulating the oxidation of glucose is so marked that a decided fall in blood sugar follows its injection; if the dose is

¹ Doctors Macleod and Banting, of the University of Toronto, were awarded the Nobel prize in medicine in 1923. Dr. Banting was lost in a plane crash during the early part of the Second World War, while on public duty.

slightly too large, alarming symptoms may develop. These can be relieved by injecting a solution of glucose or, for more prompt action, by an injection of epinephrine to stimulate the mobilization of glucose from glycogen. This illustrates the antagonistic action of these two hormones, which tend to regulate each other under normal body conditions.

Diabetes; Glycosuria. In the disease called diabetes mellitus, carbohydrate metabolism is deranged; the ability to oxidize glucose is lost or impaired, the blood-sugar level rises, and glucose appears in the urine (*glycosuria*). But a positive test for sugar in the urine does not necessarily indicate diabetes. The normal human kidney is able to retain blood sugar up to a certain level (say 160 mg per 100 ml) but passes it into the urine when this *renal threshold*—which varies in different individuals—is exceeded. This can happen with a healthy person, shortly after eating a large amount of candy, for example; thus glucose may be introduced too rapidly to be disposed of by the normal regulatory mechanisms of oxidation and storage as glycogen.

27-25 Sex Hormones. The hormones which control the development and maintenance of the male sexual organs and accessory characteristics, such as growth of the beard and deepening of the voice at puberty, are called *androgens* (Gr., *andros*, man or male). The most powerful which has been isolated is testosterone:

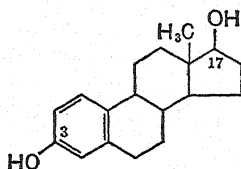


Testosterone, $C_{19}H_{28}O_2$

It is secreted and passed directly into the blood by cells of the testicle quite distinct from those which produce the sperm. This production of testosterone is under the control of another hormone which originates in the anterior lobe of the pituitary gland. Synthetic testosterone is prepared by chemical reactions from cholesterol and is ordinarily used in the form of its propionic acid ester. Methyltestosterone, similar in action and in synthetic source, has a CH_3 group in place of the C^{17} hydrogen atom of testosterone.¹

Estradiol is a hormone produced by the human ovary. This secretion, like that of the testicles, is under the control of steroid hormones from the pituitary gland. Estradiol regulates the estrus cycle and, to a large extent, determines the secondary sexual characteristics of the female. It is available in crystalline form:

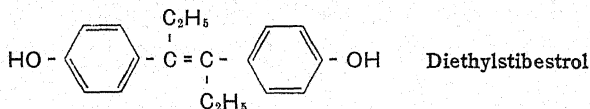
¹ The hydrogen atom on C^{17} is not shown in the formulas for testosterone and estradiol because this would violate the accepted conventions for the type of formula we are using (cf. footnote 2, page 546).

Estradiol, $C_{18}H_{24}O_2$

This compound differs from all the steroids previously mentioned in that ring A (cf. Sec. 27·18) is aromatic; consequently, the OH group on C^3 is phenolic and weakly acidic. It is interesting to note also that the *cis-trans* isomer of estradiol, in which the directions of H and OH on C^{17} are reversed, has little estrogenic activity.

Estradiol is but one of several natural estrogens of closely related structures and similar functions but differing considerably in potency; these include estriol and estrone, in both of which ring A is aromatic. *Progesterone*, the pregnancy hormone originating in the corpus luteum and also produced synthetically, has a structure much closer to that of testosterone; it differs only at C^{17} , where an acyl group replaces the hydroxyl atom found there in testosterone.

Diethylstilbestrol is of interest as a nonsteroid compound, synthesized from ordinary chemical intermediates, which has marked estrogenic activity. It is used extensively in medicine to compensate for deficiencies in the normal production of estrogens.



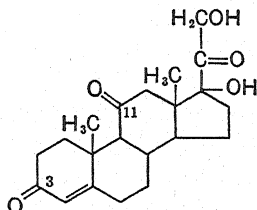
Diethylstilbestrol

27·26 Cortisone; ACTH. We have noted that epinephrine is produced by the medulla or *inner* portion of the adrenal glands. The *cortex* or rind of these glands is entirely different in its embryology and its function. Damage to it can give rise to what is known as Addison's disease. When it is completely removed from experimental animals, death follows shortly unless suitable extracts of the cortex are supplied. This is part of the evidence which led to the conclusion that the adrenal cortex must be the source of one or more highly important hormones.

The hormones of the adrenal cortex have been studied intensively for years by groups headed by E. C. Kendall of the Mayo Clinic and T. Reichstein of the University of Basle.¹ Twenty-eight different crystal-

¹ The Nobel prize in medicine for 1950 was awarded to Kendall and Reichstein, chemists, and P. S. Hench, a physician, for "their discoveries regarding the hormones of the adrenal cortex, their structure, and biological effect." The special service of Dr. Hench (of the Mayo Clinic) was in establishing the value of cortisone in the treatment of rheumatoid arthritis and other diseases.

line compounds were isolated from extracts of the cortex, only four of which were found to be active in the body. In 1936, Kendall and Reichstein independently announced the isolation of the compound now known as cortisone. The structure was established to be



Cortisone, $C_{21}H_{28}O_5$.
Cortone

Gradually, enough of the compound became available to test its properties. It was found, as expected, to have a favorable effect in Addison's disease and to exert a powerful action on carbohydrate and protein metabolism. Quite unexpectedly, it developed that cortisone is valuable in the treatment of rheumatoid arthritis (a disease formerly regarded as incurable) and various other diseases including asthma, leukemia, etc. Cortisone is now being manufactured (1951) at the rate of several thousand grams a month, with desoxycholic acid from ox bile as the starting material. The original method is said to have required 37 different steps and, while new discoveries have shortened this series to some extent and provided better yields, there continues a persistent search for a precursor with a structure closer to that of the product. A plant steroid found in an inedible yam which grows wild in Mexico is believed to offer possibilities.

ACTH (abbreviation for *adrenocorticotrophic hormone*) is a hormone secreted by the pituitary gland. The name attempts to describe its function, which appears to be that of stimulating the adrenal cortex to secrete cortisone. ACTH is available in small experimental quantities by extraction from hog pituitaries. Like insulin, it is a protein hormone. When injected into the body, it produces effects similar to those of cortisone. Investigation of the effects of both compounds upon various diseases is extremely active, as well as the search for a more abundant supply of ACTH.

Epinephrine, secreted by the medulla of the adrenal gland, can stimulate the anterior lobe of the pituitary to secrete ACTH; the latter stimulates the adrenal cortex to secrete cortisone—which, in turn, suppresses the activity of the pituitary. This is one more example of the balanced controls which the various organs of the body maintain through hormones which they secrete. Many others are well recognized.

ANTIBIOTICS

Protection of the human body against the invasion of microorganisms is one of the most important factors in maintaining life and health. We have seen that much has been accomplished toward this end by chemotherapy based on arsenicals, quinine and synthetic antimalarials, and the sulfa drugs. A further powerful weapon, more recently developed, is the use of *antibiotics*—organic compounds of biologic origin, produced by molds, fungi, etc. Many such compounds strongly inhibit the growth of bacteria (for the most part they are bacteriostatic rather than bactericidal) but are toxic to man also. Penicillin and a few others of low toxicity to man are being used widely and successfully to combat bacterial infections within the human body.

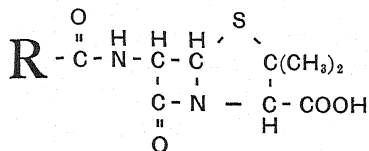
27-27 Penicillin. In 1929, Alexander Fleming noticed that clumps of bacteria in a culture dish were dissolving around a spot where a mold spore happened to have fallen and begun to grow. The inference was that the mold must be producing an antibacterial agent. This observation led by slow stages to the isolation of the *penicillin* produced during the growth of molds (*Penicillia*), to the recognition that penicillin can be used effectively in the human body against a wide variety of bacterial infections, and finally to its large-scale manufacture and use in medicine.¹

All commercial penicillin is produced by the growth of selected strains of molds (*Penicillium chrysogenum* or *Penicillium notatum*). The original laboratory method using bottles and flasks has grown into steel tanks holding up to 15,000 gallons. The fermentation medium is a solution obtained by steeping corn in water and fortified with milk sugar. Phosphates and other salts are added to meet the nutritional requirements of the mold, and the pH is carefully adjusted to about 5.5. After steam sterilization and subsequent cooling to 24°C, the medium is inoculated with a carefully grown culture of mold spores. Sterile air is passed in during the 48- to 72-hour period of growth with the temperature maintained carefully at 24°C. As the mold multiplies, penicillin is produced in the solution. When the proper stage is reached, the mold is filtered off and penicillin extracted by amyl acetate or chloroform.

¹ It is stated that early in 1942 there was not enough isolated penicillin in the world to treat a single patient. Under the stimulus of wartime needs, methods of production were developed rapidly. Continuing growth of manufacture and use is shown by the United States production of penicillin salts for 1948, 1949, and 1950 which amounted to 160, 250, and 430 thousand pounds, respectively.

Penicillin is still measured by physicians in "units." One milligram of the sodium salt of penicillin G equals 1667 units; or, 100,000 units weigh 0.06 gram. Daily treatments are of the order of 300,000 to 600,000 units. The present (1951) wholesale price is about 75 cents per gram of penicillin salt.

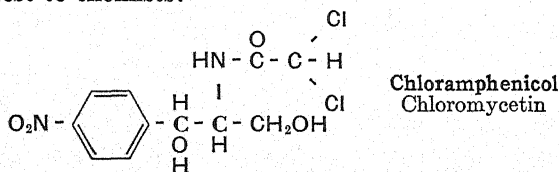
27-28 The penicillin obtained is a mixture of at least five different compounds, all of which have the following fundamental structure:



The difference is in the group R. In penicillin G, the preferred form, this is the benzyl radical; in penicillin K, which is least desirable, R is the *n*-heptyl radical. It has been learned that a marked increase in the proportion of penicillin G can be obtained by including in the culture medium a substance such as phenylacetic acid which the mold is able to utilize in producing benzyl groups. Varieties of penicillin not ordinarily formed have been obtained by supplying the molds with other chemicals. But nothing has yet been found which serves as a precursor for the part of the molecule containing the reduced thiazole ring.

Penicillin is now ordinarily used in the form of crystalline salts, such as the potassium salt of penicillin G. A favored form for intramuscular injection is the sparingly soluble salt with the base procaine; the slow release of penicillin maintains effective blood concentrations for 24 hours or longer.

27-29 Other Antibiotics. The discovery of penicillin and of its widespread usefulness has been followed by an intensive search for other useful products of the earth's microbiological population—molds, bacteria, fungi, etc. Hundreds of these products have been tested and the great majority found too toxic to higher animals to permit their medicinal use. But the quest has been rewarded already by the isolation of several compounds of the utmost importance as chemotherapeutic agents against many strains of bacteria. Those produced and used extensively include streptomycin, dihydrostreptomycin, terramycin, aureomycin, and chloramphenicol. Apart from its medicinal value, the last of these is of special interest to chemists:



It is the first antibiotic to be synthesized on a commercial scale (benzaldehyde is the starting material), all the others being obtainable only as microbiological products. Chloramphenicol is said also to be the first

natural compound known to contain a nitro group or a dichloroacetyl group.

Neither antibiotics nor any other agents now known are effective against such *virus* diseases as the common cold or against some major afflictions of unknown or uncertain origin such as poliomyelitis and cancer. Prediction is outside the province of physical science. It is encouraging, however, to recall that when the first edition of this textbook was published in 1936 the possibilities of the sulfa drugs were just beginning to be suspected and the future of antibiotics had not even been conceived.

APPENDIX

THE IDENTIFICATION OF ORGANIC COMPOUNDS

A.1 Work on the identification of organic compounds may be regarded as a process of crystallizing a student's knowledge of organic chemistry. No type of study is better adapted to emphasize the relations between structure and properties, both chemical and physical; at the same time, it affords a useful review of the general reactions by applying them from the analytical rather than from the synthetic point of view. As elsewhere, laboratory work is invaluable; but, even in the absence of extended practice, much may be gained by studying the principles underlying the procedures and applying them to the solution of suitable problems.

The identification of an *inorganic* compound is simplified by ionization in solution. Regardless of the compound from which it comes, each species of ion exhibits its own properties, by which it may be recognized. The different ions for which tests must be applied rarely exceed thirty to forty, and the identification of the original compound is not difficult when its ions have been recognized. *Carbon* compounds, on the contrary, are seldom ionized, and the work of identification has hardly commenced when the elementary composition has been established.

While it may safely be assumed that there is little chance of encountering most of the 500,000 organic compounds that are known, at least 2000 to 3000 are relatively common. Most of these the student will not have examined in his previous work; probably he has not even seen or heard their names. Hence, he may be pardoned if he is somewhat dubious when told that he is expected to *identify* a certain number of these compounds.

A.2 Identification vs. Recognition. A careful distinction between these two terms will serve to clear the ground and point the way toward success. We recognize (L., *re*, again, + *cognosco*, to know, thus *to know again*) a man by comparing his features, mannerisms, and other personal characteristics with our *memory* of a previous observation. We are convinced that he is the person remembered if enough of these agree, or even if a single one is sufficiently characteristic, as the voice of an intimate friend over the telephone. In like manner, people who have worked with phenol may be able to know it again by its odor. But neither a student nor a professional chemist can have had the detailed previous

knowledge of the great majority of organic compounds that is necessary in order to *re-cognize* them.

On the other hand, it is the daily business of police and detectives to identify persons whom they have never seen. This they do by comparing the person with an accurate *description*. In a manner quite similar, we can *identify* an organic compound never previously encountered by comparing its observed properties with those of some substance accurately described in the literature.

A-3 The Process of Elimination. Probably the detective will finally identify his man by Bertillon measurements and finger-prints; but, for obvious reasons, he cannot subject every man in the city to these tests. Instead, he proceeds to *eliminate* as quickly as possible all the persons who could *not* be the one who is wanted; thus, the field is narrowed down to a few suspects who may be rounded up and tested. The final identification of an organic unknown likewise involves the accurate comparison of its properties with those of a recorded compound. Such a comparison with any one compound is a comparatively simple matter, but making it with each of several thousand compounds is unthinkable. Hence, identification by comparison must be preceded by a *systematic* process of elimination. The individual steps in this process are briefly outlined below. By following this procedure, class after class is eliminated and the field of investigation is narrowed down, rather rapidly, to a few remaining possibilities. Then—and then only—is it profitable to commence that detailed comparison between observed and recorded properties upon which the final proof of identity depends.

A-4 Purity of Specimens. A great pioneer¹ in the systematic identification of organic compounds prints in large type at the beginning of his directions: "Establish the presumption that the unknown is really a pure compound before attempting to identify it. If it is not homogeneous, purify it. The constituents of an unknown mixture cannot be satisfactorily identified prior to their separation." The need for this warning depends upon the ease with which even small amounts of certain impurities may mask the true properties of a substance. Traces of a highly colored impurity may lead to a fruitless search through lists of colored compounds; a small amount of some highly reactive impurity may give positive tests with reagents having no effect whatever upon the chief substance present.

¹ Samuel Parsons Mulliken (1864–1934). His four-volume work, "A Method for the Identification of Pure Organic Compounds," was published by John Wiley & Sons, Inc., New York, between 1904 and 1922. While out of date in the sense that it does not list some compounds that have more recently become common, it remains of great practical value. Two volumes have been revised by Huntress (1941 and 1948).

Melting points and boiling points are usually relied upon to establish the presumption of purity. If a solid melts sharply and, particularly, if the melting point is not materially changed by recrystallization, it is probably pure. Because of the existence of constant-boiling mixtures, a definite boiling point is not conclusive proof of purity; but, aside from this possibility, a liquid may be regarded as sufficiently pure if all of it distills within a very narrow temperature range. In addition to its bearing on the probable purity of the substance, an accurate melting or boiling point has the further advantage of *eliminating* all the many compounds to which the observed constant does not correspond.

The separation of unknown mixtures involves the same principles and technique used for separating and purifying organic compounds in general. But the successful application of these methods to a mixture of *unknown* composition is often one of the most difficult situations encountered in the laboratory. For this reason, the student beginning work on the identification of organic compounds is usually supplied with unknowns which are sufficiently pure as furnished or which may be rendered so by a simple recrystallization or distillation.

A.5 Qualitative Analysis for the Elements. As soon as an unknown substance has been purified, it should be examined to determine the chemical elements of which it is composed. This is done at once because the results expedite the process of elimination and exclude many useless tests. If, for example, the presence of nitrogen is established, all non-nitrogenous compounds are immediately excluded; conversely, *proof* that nitrogen is *absent* excludes from consideration all compounds containing that element.

If the substance is known to be organic, a test for carbon is unnecessary and one for hydrogen is rarely profitable. It would be desirable to test for oxygen but, unfortunately, there is not available any direct and generally applicable method.¹ In practice, the qualitative elementary analysis of an organic compound is usually limited to testing for the halogens, nitrogen, and sulfur; the method for doing this, following a preliminary disruptive fusion with sodium, has been outlined. For the detection of metals, *e.g.*, in salts of organic acids, a portion of the substance is decomposed by heating in air until all carbon has burned away; any residue is dissolved in water or dilute acid and tested by the usual procedures for the qualitative analysis of inorganic compounds.

The tests just outlined owe their value to the fact that they may be used to prove the presence—or absence—of a particular element, *regard-*

¹ There is a *classification* test with Ferrox paper which is positive to *nearly* all oxygen-containing organic compounds and negative to hydrocarbons and their halogen derivatives. (See Shriner & Fuson, "The Systematic Identification of Organic Compounds," John Wiley & Sons, Inc., New York, 3d ed., 1948, p. 99).

less of the structure of the original substance. Conversely, the recognition of an element by these means tells nothing as to how it was united in the organic molecule. But, once the presence of an element is known, portions of the original substance may be examined to gain that information. Thus, if nitrogen were recognized, it would be in order to test portions of the unknown for the nitro group, the amino group, etc. Such tests are a part of the process of *classification* described below.

A-6 Elimination by Solubility Relations. All hydrocarbons are substantially insoluble in water; hence, if a given substance is water-soluble, it is *not* a hydrocarbon, whatever else it may be. Again, if a water-insoluble compound dissolves in sodium hydroxide, its acidity is established and neutral compounds and bases are eliminated; if, further, it does not dissolve in sodium bicarbonate solution, most carboxylic acids are eliminated and it is probably a phenol. These simple examples illustrate the value of solubility tests in the process of elimination.

In the systematic classification of compounds by solubility relations the solvents ordinarily used are: water, ethyl ether, 5 per cent sodium hydroxide, 5 per cent sodium bicarbonate, 5 per cent hydrochloric acid, cold concentrated sulfuric acid, and 85 per cent phosphoric acid. Directions for making the tests and discussions of the conclusions which may be drawn from the results are contained in various laboratory manuals especially written for this kind of organic laboratory work. These may also contain tables in which the more common substances belonging to each solubility group are arranged in the order of their melting or boiling points.

Details are beyond the scope of this summary. It should be pointed out, however, that few substances, if any, are absolutely insoluble in a specific solvent and not many are miscible in all proportions. Hence *soluble* and *insoluble* are only relative terms which can have little meaning unless the tests are made semiquantitatively and interpreted in the sense defined by the author of the work consulted.

A-7 Classification by Chemical Tests. The elementary composition of an unknown and its solubility relations eliminate from consideration many large groups of compounds. In addition, they may give useful positive indications of the presence of certain groups. It next becomes necessary to apply tests that may confirm these indications or otherwise furnish evidence for the presence of specific groups.

The tests employed are all based upon general reactions which, in the previous study of the subject, have been found most characteristic of the different functional groups (OH, COOH, SO₂OH, CHO, NH₂, etc.). For example, suppose a compound containing nitrogen is insoluble in water but dissolves in dilute HCl, thus indicating that it is a base. From this evi-

dence, it is very probably an *amine*, and further tests are in order to determine whether it is primary, secondary, or tertiary. The commoner tests for the most important functional groups have been outlined in the chapters where simple compounds containing these groups were described.

A-8 The Process of Comparison. All the procedures outlined above have as their main objective the exclusion of compounds that are *unlike* the one under examination. When this process has been pushed as far as possible, the next step is to find out what known compounds it *resembles*. This involves what is usually described as "consulting the literature."

In view of the enormous volume of chemical literature,¹ consulting it is entirely impracticable except through the aid of data which have been assembled and arranged for this particular purpose. As a matter of fact, the identification of organic compounds, as a recognized part of undergraduate instruction in chemistry, is a relatively new thing. It did not exist, and it could not exist, until the essential information had been made conveniently accessible. This classified information is provided or referred to in the appropriate laboratory manuals. From the standpoint of identification, searching the literature usually means consulting such compilations and using the data intelligently.

By combining the information obtained from laboratory tests with that furnished by tables, it is usually possible to create a presumption that the unknown substance is identical with one of two, three, or four compounds that are there described. Definite proof of its identity with one of these *may* be established by the accurate determination and comparison of several physical constants;² in general, however, it is both quicker and more certain to establish identity by preparing a characteristic derivative.

A-9 Derivatives for Final Identification. The practical use of preparing a "suitable derivative" in the final identification of an organic compound is best explained by a specific example. Assume that the

¹ The great reference work of the organic chemist is Beilstein's "Handbuch der organischen Chemie"; the fourth edition consists of 27 volumes and two series of supplements. This work is invaluable in chemical research; but, from the standpoint of practical identifications, to look here is to look for a needle in a haystack. Other valuable tables of organic compounds, including those in the common "hand-books," are likewise of little use in identification, since they are not arranged for that purpose.

² All other means failing, it is sometimes possible to complete an identification by making what is known as a *mixed melting point*. This depends upon the fact that the melting point of a pure compound is *lowered* by the presence of a foreign substance. If there is a strong presumption that the unknown is a particular substance and a pure known specimen of the latter is available, approximately equal portions of the two are mixed intimately and the melting point of the mixture is determined. If this is the same as that of the pure specimen, identity is highly probable.

substance under examination is a liquid, boiling at about 116°C, practically insoluble in water, containing no elements other than C, H, and O; it has been classified as an alcohol by suitable preliminary tests. Tables show two¹ relatively common alcohols answering to this description:

	Boiling point, °C	<i>d</i>	n_D^{20}
(I) <i>sec</i> -Amyl alcohol.....	119.5	0.809	1.4072
(II) 3-Pentanol (diethyl carbinol).....	115.6	0.815	1.410

Obviously, these differences in physical properties are not sufficient to make a conclusive differentiation. But the tables show further that (I) gives an ester of 3,5-dinitrobenzoic acid melting at 61°C, while the corresponding ester formed by (II) melts at 97°C. Hence, if the unknown alcohol is converted into its 3,5-dinitrobenzoate, the melting point of the latter will establish identity.

This illustration also suggests some of the requirements of a suitable derivative: (1) It should be prepared by a reaction which gives a good yield of a compound that can be readily purified; in practice, this means that the derivative must be a solid. (2) If possible, it should be prepared by a *general reaction* which can be expected to yield a definite product with *each* of the substances under consideration; this is illustrated by the example just cited. (3) It must have physical or chemical properties that permit an *absolute* differentiation between the several possibilities; that is, there must be a considerable "spread" between the melting points of the products that would be formed by the different compounds under consideration.

A-10 Derivatives that are *solids* are selected for preparation because they are more readily purified and because a melting point is more accurate and more reliable than a boiling point. In order that it may be easily isolated and purified, the derivative should be practically insoluble in cold water but easily crystallizable from hot water, alcohol, or some other readily available solvent. It must be a compound which, when purified, melts sharply and without decomposition.

In the example given above, it will be noted that, of all the many esters of the two alcohols that might be prepared, the esters of the relatively rare, 3,5-dinitrobenzoic acid were suggested. The purpose was to

¹ *n*-Butyl alcohol (b.p. 117.7°C) is more likely to be encountered than either of these two, but can be eliminated by the Lucas or the haloform test. If not thus excluded, it can be differentiated from *sec*-amyl alcohol by its 3,5-dinitrobenzoate (m.p. 64°C). The latter derivative would not serve to distinguish it from 3-pentanol; but one could prepare its phenylurethan which melts at 57°C while that of 3-pentanol melts at 48°C.

obtain a *solid* product. Among the esters of any lower alcohol, boiling points increase with the molecular weight of the acid; but practically all the esters with aliphatic acids are liquids and this is true also of those formed with the simpler aromatic acids, *e.g.*, ethyl benzoate and ethyl salicylate are liquids. However, nearly all the lower alcohols yield solid esters of 3,5-dinitrobenzoic acid. When an alcohol contains several hydroxyl groups, it is easier to find a solid ester; thus, ethylene glycol *dibenzoate*, glycerol *tribenzoate*, and glucose *pentaacetate* are all solids.

In general, the most important factors that are utilized in producing *solid* compounds are *increase in molecular weight* and the introduction of *aryl* groups. The latter have a specific effect, aside from the corresponding gain in molecular weight. This is notably true when they have one or more nitro groups attached; hence, the frequent use, in preparing derivatives, of such reagents as 2,4-dinitrophenylhydrazine and *p*-nitrobenzyl chloride.

Laboratory manuals for the qualitative identification of organic compounds contain lists of the most desirable derivatives, their melting points, and directions for their preparation and purification.

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